Elements of Genetics

MENDEL'S LAWS OF HEREDITY
WITH SPECIAL APPLICATION TO MAN

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ELEMENTS OF GENETICS

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PREFACE

This book is designed especially for college students in genetics It is the outgrowth of study on the part of the writer in connection with teaching the subject over a period of many years. Although written primarily for use as a text and reference work, it is hoped that the large amount of material on man and the domesticated plants and animals will make it of interest and value to the general reader.

The aim has been to present a clear and readable account of the elements of the science of genetics. In addition to a full explanation of the classical laws of Mendel and of the supplementary principles of heredity discovered since Mendel's time, there is included a thorough discussion of the roles of heredity and environment as cooperating factors in the development of the individual organism.

The historical approach has been adopted as the one most likely to gain the interest of the reader Numerous historical references are found in each chapter, it is felt that a knowledge of the development of a science is of particular interest and importance to the beginning student A separate chapter on the rediscovery of Mendel's work has been introduced because of the human interest and cultural value of the facts surrounding this episode. Similar reasons have prompted the inclusion of two rather long chapters on the heredity of human traits, as well as an English translation of Mendel's autobiography.

A glossary of terms most commonly used in genetics has been appended for the convenience of the reader.

Genetics is one of the youngest and most vigorous branches of biology. Its growth in recent years has been remarkable, especially with respect to the application of principles of genetics to microorganisms, natural populations, and man. Important new discoveries have been made in the biochemistry of gene action and the chemical induction of mutations. The author's aim in the present revision of this book is to incorporate the most interesting and significant of the recent advances and to bring the discussion of all topics up to date. The entire text has been given a thorough revision, and important changes and additions have been made in every chapter.

The chapters on Linkage and Crossing Over, The Gene and Mutation, Heredity and Evolution, and Human Heredity have been extensively rewritten. The discussion of Multiple Alleles now receives a separate chapter heading Two entirely new chapters, Domesticated Plants,

and Domesticated Animals, have been added These chapters consist of brief biographies of some of our most important domesticated species, accompanied by lists of well-established Mendelian characters for each of the selected species Since such material is often not readily accessible, owing to its wide dispersal in books, monographs, and journals, these two chapters, it is hoped, will prove especially useful Students of agriculture and animal breeding should find these additions of special interest and practical value

Lists of questions and problems have been included at the end of each chapter; these have been revised and enlarged for the present edition. The problems represent considerable range in difficulty. Usually, the easier problems appear at the head of the list and the more difficult ones at the end The general purpose in the preparation of the questions and problems is the development of a mastery of the principles and the stimulation of logical thinking

Special pains have been taken in the selection and preparation of many new illustrations for this edition. Authors and publishers have been most generous in permitting the reproduction of illustrations and tables from their publications Acknowledgment of the sources of such material is gratefully given in the legends of figures and footnotes to tables.

I wish to express my gratitude to the following persons for special material or assistance on matters that lie within their particular fields of interest and authority: Dr Meta S. Brown, Cotton Investigation Section, Department of Agronomy, Agricultural and Mechanical College of Texas; Dr. Cuthbert Dukes, Research Department, St. Luke's Hospital, London; Dr. Halbert L. Dunn and Mr. Sam Shapiro, National Office of Vital Statistics, Public Health Service, Department of Health, Education, and Welfare, Washington; Mr. Jan-Albert Goris, Commissioner of Information, Belgian Government Information Center, New York; Dr Hans Gruneberg, Reader in Genetics in the University of London; Dr. James B. Hamilton, Department of Anatomy, College of Medicine, State University Medical Center at New York City; Professor F. B. Hutt, New York State College of Agriculture, Cornell University; Dr. Donald F. Jones, Department of Genetics, The Connecticut Agricultural Experiment Station, New Haven; Dr. R L. Knight, East Malling Research Station, Kent, England; Mr. C A. Krug, Director, Instituto Agronomico, Departamento da Producão Vegetal, Campinas, Brazil; Professor Alfred Kuhn, Max-Planck-Institut fur Biologie, Tubingen, Germany; Dr. William G. Lennox, The Neurological Institute of the Children's Medical Center, Boston; Professor D. T. Morgan, Jr., Department of Botany, College of Agriculture, University of Maryland; Professor C. Pavan and Mrs M. E Breuer, Department of Biology, University of São Paulo, Brazil; Professor Lionel S. Penrose, The Galton

Laboratory, University College, London; Professor M. M. Rhoades, Department of Botany, University of Illinois; Dr. Leo Sachs, Department of Experimental Biology, Weizmann Institute of Science, Rehovoth, Israel; Dr E. R Sears, Bureau of Plant Industry, Soils, and Agricultural Engineering, U S. Department of Agriculture, Columbia, Missouri; Dr. Landrum B. Shettles, Columbia-Presbyterian Medical Center, New York; Dr. H. A. Spoehr, Department of Plant Biology, Carnegie Institution of Washington, Stanford, California; Dr. B. M. Slizynski, Institute of Animal Genetics, University of Edinburgh, Scotland; Dr. W. M. Stanley, Virus Laboratory, University of California, Berkeley; Dr. John W. Thieret, Curator of Economic Botany, Chicago Natural History Museum; Dr David H. Thompson, Senior Naturalist, Cook County Forest Preserves, Illinois; Dr. Fritz Veit, Director of Libraries, Chicago Teachers College; Professor Orland E White, University of Virginia; Dr Alexander S. Wiener, Senior Bacteriologist (Serology) to the Office of the Chief Medical Examiner of New York City. I am indebted to Professor R A. Fisher, also to Messrs. Oliver and Boyd, Ltd , of Edinburgh, for permission to reprint Table 2 from their book "Statistical Methods for Research Workers."

I am deeply grateful to Professor Sewall Wright for his critical reading of much of the material in this and earlier editions and for his many valuable suggestions. Special thanks are due to my wife, Alta R. Colin, who made some of the drawings and read parts of the text, to the great improvement of the clarity of the language Many of the drawings are the work of Virgil Vogel, to whom I express sincere appreciation I also wish to thank my sons Edward and Galen for their help in the preparation of some of the drawings.

As in the past, the author will value highly all suggestions for changes or additions that readers may think desirable.

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CONTENTS

TO THE STUDENT

WHAT IS GENETICS?

Genetics is that branch of biology which deals with the laws or principles of heredity and variation as observed in plants, in animals, and in man Its function is to discover and explain the mechanism of the origin and transmission of the hereditary substances from one generation to the next, as well as the process of interaction of these hereditary substances with the internal and external environment of the individual during its development.

Genetics is one of the newest subdivisions of biology. It originated as a distinct field of study in 1900 with the rediscovery of Mendel's pioneer experiments Since that date it has grown at an accelerating rate through the labors of many investigators in field and laboratory in all the major countries of the world Today it is one of the most active and fruitful branches of the biological sciences

Two subdivisions of biology closely related to genetics are cytology (the study of the cell) and embryology (the study of reproduction and development) These subjects are covered more or less adequately in books on general biology

REASONS FOR STUDYING GENETICS

Some of the advantages to be gained from a study of genetics are the following.

√1 Genetics is concerned largely with an explanation of the differences existing among individuals, hence it is of great value to persons who are contemplating marriage. It helps in analyzing the potentialities of individuals already living as well as in predicting the traits of future offspring from a given mating.

Most persons who marry contemplate the birth of children Genetics is of great assistance to the parent and the teacher in understanding differences among children Such understanding is indispensable for the proper adjustment of methods of teaching and care of the young in accordance with the individual needs of children.

/ 2 Genetics is making valuable contributions to the improvement of domesticated plants and animals of economic importance. Through the application of genetic principles, it is now possible to support in a given geographical region a much larger human population than could have

been done prior to the development of the science of genetics Our subject, therefore, has far-reaching social implications

3 Applications of genetics are finding their way into medical practice and into measures for the improvement of the health and intelligence of future generations In the years that lie ahead we may confidently expect increased activity in this direction. As citizens, we shall be called upon to form judgments on issues affecting the biological improvement of the population In the present book special emphasis is given to the applications of genetics to man

SUGGESTIONS FOR STUDY

The amount of reading required for a beginning course in genetics is not extensive *Intensive* study, however, is essential for success in the course. Such study involves reading and rereading until a thorough grasp of the principles is obtained Each principle is illustrated by examples described in the text. The problems and questions at the end of each chapter are designed to furnish a check on your mastery of the principles Genetics resembles mathematics in that one topic is built upon another in logical order, therefore never leave one topic until you are satisfied that you have mastered it

Although extensive reading is not required, some additional reading is highly recommended, especially for those who are majoring in the biological sciences The references given in the footnotes of the text will be found especially useful as a guide to supplementary reading.

Terminology. Like other specialized branches of learning, genetics has its own terminology The number of terms required in this course is not excessive, and most of the terms will be used again and again. Care has been taken to explain in the text and to illustrate each new term at its first introduction Try to make each of these words a part of your own vocabulary. Do not hesitate to commit definitions to memory; in this respect the glossary at the back of the book will prove helpful Terms, nevertheless, are merely tools for use in clear thinking *Our most important objective should be to develop the ability to think logically about the facts and principles of the subject we are studying and to acquire the skill to solve problems as they are presented to us*

Read Chapter 1 carefully in order to acquire a background for an appreciation of Mendel's discoveries. The experiments of Mendel constitute a brilliant example of the application of the scientific method to a specific problem The inductive method is one of the chief contributions of science to civilization

Study Chapter 2 as a unit Give special attention to the illustrative examples therein described If you understand these you should be able to work the problems and answer the questions at the end of the chapter.

The idea of probability is of fundamental importance in genetics It is not especially difficult, but the train of thought may be new to you, and if so, intensive study will be in order

Written Work. In case you use the checkerboard method as illustrated on page 13 of Chapter 2, and one of the parents in a mating is purebred (homozygous), use only one row of squares for that parent In other words, use only as many squares each way as there are *kinds* of eggs or sperms

Your resulting ratios should always be expressed in the *lowest* terms, e g , 1 : 1 rather than 2 :2. Where actual numbers of offspring are given, as in Problem 2, first decide in your own mind what simple ratio is represented by the offspring, keeping in mind at all times that with very small numbers the offspring may not fit any simple ratio closely. Try to distinguish between what is possible and what is probable

Most of the problems in Chapter 2 are designed to give you an opportunity to apply the principle of probability Keep in mind the rule that *the chance of two or more independent events occurring simultaneously is equal to the product of the chances of the events occurring separately* Likewise, *if one event can occur only after another has occurred, then the probability that both will take place is equal to the product of the two probabilities* If you have any difficulty with any of the problems involving probability, review the discussion and the examples given in the text.

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MENDEL: STUDENT, PRIEST, TEACHER, INVESTIGATOR

In the history of man's progress toward an understanding of the laws of nature, no story has higher dramatic interest than that of the discovery of the laws of heredity This story centers about the life of a great man, Gregor Johann Mendel,[1] born July 22, 1822, in Heinzendorf, a village in the Sudeten region of Silesia, at that time a part of the Austro-Hungarian Empire.

Mendel was the second child of a successful farmer and fruitgrower. His ancestry was probably a mixture of German and Czech In the village elementary school Mendel showed such talent that at the age of eleven he was sent to the upper elementary school at Leipnik, a town about thirteen miles distant. Here, too, he did well and reached the top of his class, with the result that at the end of 1834 he was sent to Troppau High School, more than twenty miles away.

While in high school, misfortunes at home compelled him, for a time, to earn his own expenses, and in the spring of 1838 a serious illness forced him to return home, where he remained until September. Mendel completed the required six years at high school and graduated in August of 1840 with an excellent record

In 1840 [quoting from a short autobiography written later] after having completed his studies at the Gymnasium his first concern was to secure the means necessary for continuing his studies In Olmütz he attempted therefore repeatedly to offer his services as a private tutor, but on account of lack of friends and of recommendations his efforts remained unsuccessful The grief resulting from these shattered hopes and the uneasy and sad prospects for the future were of such a

[1] As authority for most of the facts on the life of Mendel I am indebted to the excellent biography "Life of Mendel," by Hugo Iltis, published originally in German, 1924, under the title "Gregor Johann Mendel, Leben, Werk, und Wirkung" and translated into English by Eden and Cedar Paul, W. W. Norton & Company, Inc., New York, 1932.

deep impact that he fell ill and had to spend a whole year with his parents to recuperate

Finally, with some financial help from one of his sisters and money earned in private teaching, he completed the two-year course at Olmutz Philosophical Institute.

Mendel's autobiography, mentioned above, consisted of four pages in longhand. It was written in 1850 to accompany his application for admission to an examination for high-school teachers Fortunately this interesting manuscript was preserved It was published in full in the original German, with a brief statement by Hugo Iltis (see Appendix A for an English translation in full)

In October, 1843, Mendel was admitted to the Augustinian monastery at Brunn in Moravia

During the time here that he was not busy with his classical and theological studies he worked with botanical and mineralogical collections in the monastery His interest in natural science grew In 1848 he completed his theological studies, and one year later accepted an assignment as substitute teacher in the high school at Znaim.

MENDEL AS TEACHER

In his high-school position at Znaim Mendel taught Greek and elementary mathematics In 1850, at the urging of his chief and colleagues, he took the examination for a teaching certificate The examination was conducted by professors at the University of Vienna. In spite of the fact that the young teacher had studied little science in school and had never attended a university he succeeded in passing the examination in physics, but failed in geology and in the classification of mammals.

The chairman of the examining committee, recognizing Mendel's native ability, recommended that he be given more training. As a result of this recommendation, the abbot of the monastery permitted him to enter the University of Vienna as a student Here he studied from 1851 to 1853, taking courses in zoology, systematic botany, paleontology, physics, and mathematics

In 1854 Mendel began his career as a supply teacher of physics and natural history in the Brunn Modern School In 1856 he came up for a second trial at the examinations, but again he failed to win a certificate. The record is not clear as to why he failed Iltis believes that he was in some way offended in the oral part of the examination and voluntarily withdrew. Whether this is true or not, it agrees with what we might expect from one of Mendel's sensitive and independent nature. The events in his later life show clearly that when he believed himself to be in the

right he could be one of the most stubborn of men. Apparently his own school authorities did not regard him as incompetent, for he remained as supply teacher for twelve more years, and then was elected abbot. With his students and colleagues he was a popular and successful teacher.



Figure 1. Gregor Mendel, 1822–1884 *(From Iltis, "Life of Mendel," W. W. Norton & Company, Inc.)*

MENDEL AS INVESTIGATOR

According to one of his colleagues, Mendel was stimulated to begin his experiments on artificial crossing of plants by the dispute with an examiner already referred to. Iltis does not accept this theory, but believes that he entered upon the experiments for their own sake. However this may be, it is well known that in those of tough mental fiber a failure in one line of endeavor merely spurs the will to succeed in some other line. Mendel's brilliant success as an investigator in succeeding years proved beyond all doubt the superior quality of his mind.

Mendel states in the introduction to his paper describing the famous experiments with peas that these experiments were suggested by results

obtained in artificially fertilizing ornamental plants in order to produce new color varieties The striking regularity with which the same hybrid forms appeared when fertilization took place between the same species led him to follow up the development of the hybrids in their own offspring This principle of the uniformity of first-generation hybrids is illustrated in the well-known case of the mule, a hybrid between the horse and the ass Mules are no more variable than the parent species from which they are derived

As the son of a farmer and fruitgrower Mendel had grown up in an atmosphere of plant and animal breeding, and he maintained his interest in plants and animals throughout life Fruits, flowers, and bees were of special interest to him In his study of botany, zoology, and paleontology at the University of Vienna he must have gone into the technical classification of plants and animals as well as into their past history, and no doubt there had developed in him a thirst for a more adequate philosophical explanation of what he saw in living nature

A number of reports of experiments on plant hybridization, including one on a hybrid between the pea and the vetch, had recently been published. Mendel may have been influenced by them. It is possible also that his interest in evolution and the origin of species was instrumental in directing the line of his researches.

MENDEL AND EVOLUTION

We do not know at what time Mendel first became interested in the growing discussion of evolution which, in 1859, burst with explosive force in the publication of Charles Darwin's book "The Origin of Species," shaking the intellectual world to its foundations. We learn from Iltis that Mendel, during his own researches, became a thorough student of Darwin's work, that he bought all of Darwin's books; and that almost all of the Darwinian literature of the 1860s and 1870s is in the library of the monastery at Brunn In a copy of "The Origin of Species" and also in a copy of "The Variation of Animals and Plants under Domestication" by Darwin, belonging to the library, there are many notes in Mendel's handwriting.

With characteristic independence of mind, Mendel did not accept Darwin's theories as adequate, although he was not opposed to evolution. And, interestingly enough, the very field in which Darwin's theories later proved to be inadequate (the field of heredity) is the one in which Mendel was to make his own great contribution. According to one of his fellow teachers, Mendel frequently tried to produce permanent variations by the transplantation of plants from their natural habitat, but the results were always negative. These experiments seem to have convinced him

that nature did not work in any such way, and that, contrary to Darwin's belief, the inheritance of acquired characters was not a factor in evolution. It is certain, however, that Mendel realized the important relationship of his own discoveries to the principle of evolution, for we find this point specifically emphasized in his paper on experiments with peas

Regrettably, Darwin never knew of Mendel and his work. A search through Darwin's extensive library, made by his son following the scientist's death, failed to disclose a copy of the paper on peas, and no reference to Mendel has ever been found in any of Darwin's writings. In the sixth edition of "The Origin of Species"[1] published in 1872, six years after Mendel made known the laws of heredity, we still find the following statement·

> The laws governing inheritance are for the most part unknown. No one can say why the same peculiarity in different individuals of the same species, or in different species, is sometimes inherited and sometimes not so, why the child often reverts in certain characteristics to its grandfather or grandmother or more remote ancestor . . .

These were exactly the questions which Mendel's experiments had answered. Had Darwin come in contact with Mendel's work the history of biology during the last third of the nineteenth century would have been quite different. Darwin's extensive knowledge of hybridization, based in part on his own experiments, would no doubt have led him to appreciate at once the importance of Mendel's work As a result, the study of evolution would have taken a more fruitful turn and Mendel would surely have received during his lifetime the recognition due him. This, however, was not to be.

MENDEL'S EXPERIMENTS WITH PEAS

In 1856, soon after his second failure in the examination, Mendel began his experiments in crossing the edible pea These were continued up to and including 1863. His breeding experiments were carried on each summer in a garden plot measuring only 20 feet by 120 feet alongside the building of the monastery (Fig 2) Again and again he writes in his letters how cramped he is in his researches During the winter months when he could not continue his experiments out of doors, it is easy to imagine him going over and over his results until he had finally formulated the laws by which his name, years after his death, was to famous.

Mendel delivered the first report of his work before the
for the Study of Natural Science on February 8, 1865. At a .

[1] Charles Darwin, "The Origin of Species," D. Appleton-Century Co.,

ing one month later he concluded his discussion. In 1866 the paper was published in the proceedings of the society. The proceedings were exchanged with more than 120 other societies, universities, and academies at home and abroad.[1]

Mendel's report fell on deaf ears. In his lectures before the society there were no questions and no discussion. The same silence enveloped the publication of his article. During the following 34 years not one person, so far as the records show, realized that here in the compass of 46



Figure 2. Garden of the Augustinian monastery at Brünn, Moravia, in which Mendel carried on his experiments with peas. *(From Shull, J. Heredity,* 1935.)

pages was revealed one of the most important laws of nature ever discovered by man. How are we to explain this apparent blindness of other scientists? An attempt to answer this question had best be deferred until after an examination of the nature of the discoveries themselves.

Mendel's choice of peas as experimental material was not an accident. He tells how important he regards the right material to the success of any experiment and gives his reasons for selecting peas: first, he found that peas were obtainable in many pure-breeding varieties; second, the flowers were well protected from the influence of foreign pollen, owing to

[1] Mendel's original paper, "Versuche über Pflanzenhybriden" (Experiments in Plant Hybridization), was published in *Verhandlungen des Naturforschenden Vereins* in Brünn, vol. 4, 1866. A reprint of an English translation by the Royal Horticultural Society of London is published and sold by Harvard University Press, Cambridge, Mass. A facsimile reprint of the original German edition was published in *J. Heredity,* **42**:1-47, 1951.

the close encasement of the reproductive organs inside the petals of the flower (Fig. 3); and third, the hybrids resulting from crossing two varieties were perfectly fertile The last fact has been demonstrated many times by other experimenters

Having decided upon peas, Mendel obtained seeds of 34 varieties from several seedsmen. These he tested out by planting over a period of two years, in order to be sure that they were pure-breeding varieties From the list of 34 he selected 22 varieties which he cultivated during the entire eight-year period of the experiments Without exception they remained constant, indicating that they were pure varieties

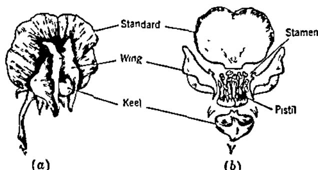


Figure 3. (a) Mature pea blossom. (b) Diagram of pea blossom showing petals, consisting of standard, wings, and keel, separated to expose the pistil and stamens The boat-shaped keel and the wings close tightly around the stamens and pistil, ensuring self-pollination

Mendel's primary object was to cross one variety with another and to observe the resulting hybrids[1] in the first and succeeding generations in order to discover the law which controlled the appearance of contrasting characteristics in successive generations Peas are normally self-fertilizing, but the production of hybrids is not difficult all that is necessary is to open the bud before the flower is fully developed, and with forceps to extract the pollen-producing organs (stamens), then the pollen, containing the male fertilizing cells, or sperms, from a plant of another variety, is at once dusted upon the upper end of the egg-producing organ (pistil) This was the technique followed by Mendel

The wall of the pollen grain soon breaks, and a pollen tube containing the sperm cell grows down, eating its way through the pistil until it finally reaches the egg in the ovary (expanded lower end of the pistil),

[1] Although the term hybrid is often applied to the offspring of two distinct species, it is used properly also, as pointed out by Mendel, for offspring of two different varieties

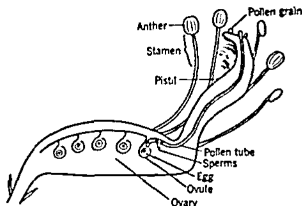


Figure 4. Diagram of pistil and stamens of the pea showing pollen tube growing down, carrying the sperm to fertilize the egg. The second sperm unites with two other nuclei (not shown) in the ovule to produce the endosperm of the seed.

where the sperm fertilizes the egg (Fig. 4). The seed which develops after cross-fertilization is a hybrid for the same reason that an animal whose parents are of different varieties is a hybrid.

REASONS FOR MENDEL'S SUCCESS

Mendel was keenly aware of the basic problems which had to be solved in order to gain an understanding of the mechanism of heredity. He has been credited by the leading contemporary British cytologist, Darlington,[1] with the successful conduct of two of "the three vital experiments" on which modern genetic principles are founded. The best known of these experiments, his work with peas, is described in the next two chapters. The second experiment, which is not widely known and is not often mentioned, led to the proof that a single pollen grain is sufficient to bring about the fertilization of the egg of a plant. The results were reported in 1870 in a letter to the German botanist Nägeli.

On the basis of experiments of leading investigators of the time, it had become generally accepted that several pollen grains were necessary for a single fertilization. If true, this would have been irreconcilable with Mendel's deductions regarding the laws of heredity resulting from his experiments with peas. Accordingly, he considered it necessary to repeat the pollination experiments. He used the same plant, the four-o'clock (*Mirabilis*), as the previous workers had used. In this plant the pollen grains are extraordinarily large. His results were directly contrary to those

[1] C. D. Darlington, "The Evolution of Genetic Systems," Cambridge University Press, London, 1939.

of previous workers. He obtained from fertilization with single pollen grains 18 well-developed seeds and from them as many plants, the majority of which were just as fully developed as those derived from free pollination A few were somewhat stunted Later in the same year, Mendel again wrote Nageli and advised him that the stunted plants had made up the loss and could not be distinguished from those produced by ordinary pollination. Mendel repeated the experiment and again obtained fertilizations from single pollen grains.

Mendel correctly explains the advantage in using a number of pollen grains. He concludes that pollen grains are not all alike in their fertilizing capacity With a number of grains there is a chance that one at least will be successful in effecting fertilization. Where several compete, he says, we may assume that always the strongest succeeds in alone effectuating the fertilization. Differences in viability and in growth rate in pollen have been abundantly confirmed in many different species of plants since Mendel's time.

Like all great discoverers, Mendel had predecessors from whom he got ideas and by whose mistakes he profited. Hybridization experiments had been done many times before with both animals and plants, including peas, but not one of the earlier experimenters had succeeded in discovering the law by which one could predict what sort of offspring a given hybrid would produce or the relative numbers of each kind Mendel clearly saw the reasons for such failures and took every precaution to avoid them.

First, he recognized the necessity of keeping adequate records A good experimenter must first of all be a good bookkeeper. He saw that he must keep separately the records for each generation and that he must carefully divide the offspring in each generation into classes according to their visible characteristics and record the exact numbers of each class

Secondly, unlike most of his predecessors, Mendel realized that the laws of heredity in a complex organism could only be discovered by concentration on one characteristic at a time. Other investigators had failed partly because of their attempt to experiment with the organism as a whole.

Finally, he recognized that the movement of the sperms to the eggs and the union of the gametes in fertilization is a complex process, extending over a considerable period of time There is always an element of chance involved in such a process, in that precise movements cannot be predicted in individual cases; hence the rule, or law, describing the union of the gametes of various sorts cannot be deduced from only a few individuals The numbers must be large enough to ensure that unpredictable, or chance, factors will cancel each other, leaving the law based upon innate differences among the gametes free to express itself. In other words,

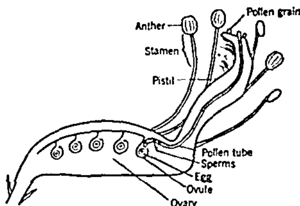


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First, he recognized the necessity of keeping adequate records A good experimenter must first of all be a good bookkeeper He saw that he must keep separately the records for each generation and that he must carefully divide the offspring in each generation into classes according to their visible characteristics and record the exact numbers of each class

Secondly, unlike most of his predecessors, Mendel realized that the laws of heredity in a complex organism could only be discovered by concentration on one characteristic at a time Other investigators had failed partly because of their attempt to experiment with the organism as a whole.

Finally, he recognized that the movement of the sperms to the eggs and the union of the gametes in fertilization is a complex process, extending over a considerable period of time There is always an element of chance involved in such a process, in that precise movements cannot be predicted in individual cases; hence the rule, or law, describing the union of the gametes of various sorts cannot be deduced from only a few individuals The numbers must be large enough to ensure that unpredictable, or chance, factors will cancel each other, leaving the law based upon innate differences among the gametes free to express itself. In other words,

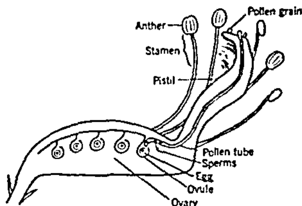


Figure 4. Diagram of pistil and stamens of the pea showing pollen tube growing down, carrying the sperm to fertilize the egg. The second sperm unites with two other nuclei (not shown) in the ovule to produce the endosperm of the seed.

where the sperm fertilizes the egg (Fig. 4). The seed which develops after cross-fertilization is a hybrid for the same reason that an animal whose parents are of different varieties is a hybrid.

REASONS FOR MENDEL'S SUCCESS

Mendel was keenly aware of the basic problems which had to be solved in order to gain an understanding of the mechanism of heredity. He has been credited by the leading contemporary British cytologist, Darlington,[1] with the successful conduct of two of "the three vital experiments" on which modern genetic principles are founded. The best known of these experiments, his work with peas, is described in the next two chapters. The second experiment, which is not widely known and is not often mentioned, led to the proof that a single pollen grain is sufficient to bring about the fertilization of the egg of a plant. The results were reported in 1870 in a letter to the German botanist Nägeli.

On the basis of experiments of leading investigators of the time, it had become generally accepted that several pollen grains were necessary for a single fertilization. If true, this would have been irreconcilable with Mendel's deductions regarding the laws of heredity resulting from his experiments with peas. Accordingly, he considered it necessary to repeat the pollination experiments. He used the same plant, the four-o'clock (*Mirabilis*), as the previous workers had used. In this plant the pollen grains are extraordinarily large. His results were directly contrary to those

[1] C. D. Darlington, "The Evolution of Genetic Systems," Cambridge University Press, London, 1939.

2

DOMINANCE AND THE LAW OF SEGREGATION

Having chosen peas as his experimental material, Mendel reduced the problem to its simplest terms by selecting for thorough study seven pairs of easily recognizable contrasting characteristics The results of his breeding experiments on these were reported in detail in his paper. The seven characteristics, all conspicuous morphological traits, are as follows.

1 Differences in the shape of the ripe seeds: either smoothly rounded or deeply wrinkled and irregular in shape

2. *Differences in the color of the cotyledons· either yellow or green*

3. Differences in the color of the seed coat. either gray-brown or white

4 Differences in the form of the ripe pods. either simply inflated, not constricted in places, or deeply constricted between the seeds

5 Differences in the color of the unripe pods: either green or yellow

6 Differences in the position of the flowers: either axial, that is, distributed along the main stem; or terminal, that is, bunched at the top of the stem

7 Differences in the length of the stem. either tall, from 6 to 7 feet, or short, from ¾ to 1½ feet

Between varieties showing sharp contrasts in the characteristics selected he made crosses in the manner previously described The offspring from the hybrids were in turn studied through successive generations.

ROUND PEAS AND WRINKLED PEAS

Let us now examine one of Mendel's experiments—an experiment that will illustrate perfectly the results he obtained, in all A variety of peas having smoothly rounded seeds was crossed with a variety having deeply wrinkled seeds. The hybrid seeds resulting from this cross were all round, like the round-seeded parent. This was true regardless of which variety was used to furnish the pollen and which the eggs

The following season Mendel planted the hybrid round seeds. From these at harvesttime he obtained 5,474 round seeds and 1,850 wrinkled seeds, or a ratio of 2.96 round to 1 wrinkled (almost a perfect 3:1 ratio).

Although the hybrids had all been visibly indistinguishable from their round parent, they were evidently not pure round, since one-fourth of their offspring were wrinkled The wrinkled character, he concluded, must in some way have been carried over in a latent form in the hybrid. Round had dominated in the hybrid, and therefore Mendel called this the *dominant* character, wrinkled had receded from view, therefore he called this the *recessive*

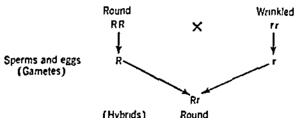
What is the explanation of the ratio of 3 1 in the third generation? Mendel's correct answer to this question deserves the highest credit, for in his day little had yet been discovered about what goes on inside of plants during reproduction, save that there was the formation of two sorts of reproductive cells (eggs and pollen cells); that the pollen cell fused with the egg in the process of fertilization, and that the fertilized egg then developed into a tiny embryo contained within the seed.

Mendel assumed the existence in each pollen cell and egg of a "formative element" (now known as a *gene*) capable of determining a character in the offspring (More accurately, a single nucleus from the pollen grain, Fig. 4, functions as a sperm in fertilization Hereafter we shall refer to this nucleus as the sperm)

Following Mendel's usage, the term *hybrid*, frequently combined with a prefix, is often used by geneticists in Great Britain and the United States to indicate an individual with one or more pairs of unlike genes; thus *Rr* is known as a *monohybrid*. Originally the word *hybrid* was applied to a cross between varieties, races, or species, and this is still correct usage Another term, *heterozygote* (*hetero*, different; *zygote*, egg), is used in genetics today to indicate an individual with one or more dissimilar gene pairs The term *homozygote* refers to an individual in which both genes of any pair or pairs under study are identical.

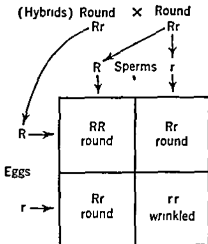
In a purebred variety the genes occur in identical pairs; these are represented by two capital letters, as *RR*, for round. In the contrasting variety, wrinkled, the genes are different from those for round, and the symbols used must therefore be different, for example *rr* for wrinkled. Following Mendel's lead there has grown up a universal custom of representing dominant genes by capital letters and recessive genes by lowercase letters. This method of symbolism is the simplest yet devised. It has many uses in dealing with problems of heredity. As a matter of economy, the single term *gamete* is often used to denote either a sperm or an egg

A cross-mating of round peas and wrinkled peas is therefore represented as follows:



The dominant gene is able to override completely in its physiological effect the recessive gene, so that all of the hybrid seeds are round like the round parent.

The union of the genes in hybrids is, however, Mendel concluded, only temporary, and when the hybrid seeds in turn are planted and eventually produce sperms and eggs, the genes *R* and *r* are liberated from the union and unite freely at fertilization in all possible combinations, as shown in the checkerboard diagram below.



Instead of showing the chance combinations of gametes by means of a checkerboard diagram, many prefer the fractional method as used by Mendel, thus $(\frac{1}{2} R + \frac{1}{2} r)^2 = \frac{1}{4} RR + \frac{1}{2} Rr + \frac{1}{4} rr$ Since the results are identical with those obtained with the checkerboard, one may take his choice.

The experimental results agree perfectly with the theory that the hybrid produces two kinds of eggs and two kinds of sperms with respect to the genes under consideration; that these occur in equal numbers; and that each kind of egg and sperm has the same chance of functioning in fertilization as the other. The hybrids, therefore, produce offspring rep-

resented by the three combinations of letters *RR*, *Rr*, and *rr* in the *genotypic* ratio of 1 *RR* 2 *Rr* 1 *rr* Since *R* is dominant over *r*, the combinations *RR* and *Rr* look alike and the *phenotypic*, or visible, ratio is 3 round:1 wrinkled



Figure 5. Fasciated or Mummy pea in fruit. The terminal flowers, and fruits, were shown by Mendel to be inherited as a recessive character; axial flowers are dominant. (*Courtesy of Orland E White and Brooklyn Botanic Garden.*)

To summarize, Mendel's first law, which has come to be known as the *law of segregation*, states that hereditary differences among individuals depend upon differences in cellular units, or genes; that these units are present in pairs in the cells of organisms derived from fertilized eggs; that each sperm and egg produced by such organisms receives a single member of each pair, so that if a given pair consists of unlike genes, two sorts of sperms or eggs, with respect to this gene, are produced in equal numbers; and finally, that at fertilization the union of like sperms and

eggs occurs with the same frequency as the union of unlike sperms and eggs.

OTHER CHARACTERS FOLLOW THE SAME LAW

In like manner with all of his other six pairs of contrasting characteristics, Mendel found that one member of each pair was fully dominant and the other was recessive. Which one was to be dominant and which one was to be recessive could not be predicted; it could be discovered only by making the cross. Mendel had no theory as to why one gene dominates the other, and even today in only a few cases have we an adequate theory of dominance. Dominance is related to the physiology of development of the organism. We shall consider the problem of gene action in a later chapter.

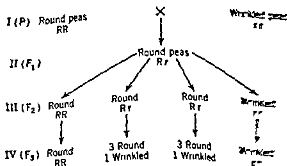
Just as with the characters round and wrinkled, the hybrids for every other pair of genes produced offspring consisting of dominants and recessives, always approximately in the ratio of 3 dominants:1 recessive.

LATER GENERATIONS OF HYBRIDS

A less critical investigator might have stopped his experiments at this point, but Mendel was not yet satisfied. *His next step was to plant the seeds produced by the third generation to see what happened.* The reader may now safely risk a prediction as to the outcome.

Mendel found in every case that the recessives, when self-fertilized, produced only pure recessives. We can see why this should be. A wrinkled seed always contains both genes *rr*; it cannot be a hybrid since the hybrid *Rr* is always round. A recessive must therefore always breed true.

With the round seeds of generation III, however, Mendel found that upon self-pollination, one-third produced nothing but round seeds; the other two-thirds produced round and wrinkled seeds in the ratio of 3 round:1 wrinkled as follows.



Mendel continued this testing process through six generations of descendants of the first hybrids, and in each generation the round seeds produced by hybrid round peas continued to appear in the ratio of one pure-breeding round to two hybrid round. It is obvious from the preceding diagram that if self-fertilization of all the offspring occurs in each generation, the proportion of hybrids in the entire population diminishes rapidly from generation to generation, while the proportion of pure types steadily increases. This, Mendel writes, confirms the observations made by other investigators that hybrids tend to revert to the parental types. Theoretically, however, the hybrids will never disappear entirely.

MENDEL'S DETERMINERS: CHROMOSOMES AND GENES

In Mendel's day modern methods of staining cells in order to make visible their differentiated structures had not been perfected, and, as far as we can learn from his paper, Mendel was unaware of any visible structure in the cells of living things capable of serving as the "formative elements." These remained for the time being as purely hypothetical entities. Not long after Mendel had published his results, however, visible structures (now known as *chromosomes*[1]) were observed regularly in cells. Some years later it was found that the chromosomes occur in pairs in all the body cells of organisms, as well as in immature germ cells, and that during formation of the eggs and sperms the chromosomes constituting each pair in the early reproductive cells separate so that each egg and sperm receives only one member of each pair. At fertilization they again come together in pairs. There is thus a perfect parallelism between the behavior and distribution of the chromosomes as we know them today and of the formative elements mentioned by Mendel. Since Mendel's time, by methods ever growing in refinement, it has been proved beyond doubt that the chromosomes contain the formative elements, or genes, which Mendel assumed to exist. The chromosomes and genes are considered in detail in later chapters.

THE BACKCROSS; PURITY OF THE GENE

The core of Mendel's discovery, as just described, is that individuals which are hybrid (heterozygous) with respect to one pair of genes always produce two kinds of eggs and two kinds of sperms, while those which

[1] The word chromosome (*chroma*, color, *soma*, body) was coined by Waldeyer, 1888, and alludes to the ready capacity of these cellular bodies to absorb basic dyes. Although chromosomes had been seen before Mendel's time, it was not until the 1870s and 1880s that their significance in cell division was finally established.

are pure (homozygous) produce only one kind. Moreover, Mendel's ratios show that the two kinds of eggs and sperms occur in equal numbers, and that at fertilization the union is as likely to take place between identical genes as between unlike genes The specific genes contained in a sperm usually have nothing to do with its ability to reach and fertilize the egg, nor do the specific genes of the egg determine its capacity for fertilization.

In the experiment in which the hybrids were tested out through six successive generations there was found no contamination of one gene by another, in spite of their close association in the same cells of the hybrid, for at the end of the experiment the hybrids were still producing pure dominants and pure recessives in the same ratio as at the beginning The purity of the gene is a point of fundamental importance Evidently the gene behaves almost as an autonomous body within the cell, being affected neither by other genes in the same cell nor by the cells of the organism as a whole. The genes remain unchanged indefinitely.

Many experiments to test this conception of the purity of the gene have been performed since Mendel's time. The most extensive of these, extending over a period of more than fifteen years, carried on at Johns Hopkins University under the direction of Professor Raymond Pearl,[1] fully confirms Mendel's results. Using the fruit fly Drosophila (Fig 6) as the experimental animal, more than 300 successive generations of descendants of a particular individual were reared Converted into human generations and allowing four generations to the century, this would carry us back farther than 5500 B.C Such an experiment is made possible by the fact that under favorable conditions the life cycle of this fly is completed within ten days

The gene chosen for testing in this experiment was one affecting the development of the wings, a recessive gene known as vestigial, the effect of which is to reduce the wings to useless stubs The experiment was begun with a normal male mated to a female with vestigial wings The hybrids all had normal wings From these hybrids and from the hybrids in each succeeding generation males were bred back to vestigial females, making what is known as *backcross matings* From each backcross mating the ratio of normal-winged offspring to vestigial-winged offspring was always 1:1. Consequently, the normal gene in the hybrids was exposed for more than 300 generations to the influence of the contrasting recessive gene—and this without showing any effect whatever of the vestigial gene on the normal gene.

The method of the backcross mating has important applications to plant and animal breeding, as well as to human beings. It is being used

[1] Raymond Pearl, Biology and Social Trends, *J Wash Acad. Sci.*, vol. 25, no 6, 1935.

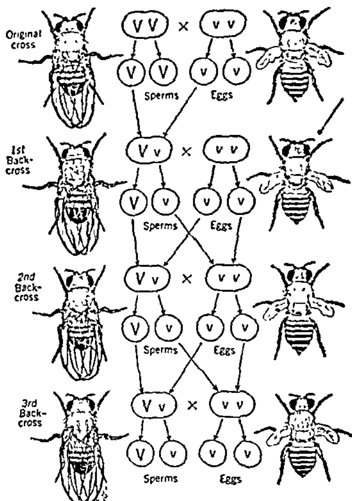


Figure 6. Diagram illustrating a backcross mating in the fruit fly Drosophila A normal-winged fly is mated to a vestigial-winged fly, the hybrid is then mated to a vestigial-winged fly, and this backcross is repeated in each generation. The ratio in each generation is 1 normal: 1 vestigial.

on a large scale to develop disease- and insect-resistant varieties in plants such as wheat, cotton, tobacco, tomatoes, potatoes, etc ,[1] an example of which will be given.

It frequently happens that an excellent variety of a domesticated plant or animal shows poor resistance to some specific disease-producing bac-

[1] Mary Thomas, "Back Crossing The Theory and Practice of the Backcross Method in the Breeding of Some Non-Cereal Crops," Commonwealth Bureau of Plant Breeding and Genetics, Cambridge, 1952.

terium or virus, or to a fungus or animal parasite. At the same time, other varieties of the plant or animal, or a related wild species, may possess high resistance to the parasite. In other respects, however, the wild species may show many undesirable traits. If the breeder could only transfer the specific resistance of the wild species to his domesticated variety, without also introducing the unwanted traits, a big increase in production would follow. This is just what the backcross method is able to do. Let us take an example from a domesticated plant in which the backcross method has been widely used—the edible tomato.

Tomatoes are native to South America, where numerous wild species and varieties exist. The more common domesticated varieties are derived from the species *Lycopersicon esculentum*. Most of the domesticated varieties are susceptible or only moderately resistant to a serious soil-infesting fungus that produces a disease known as fusarium wilt. A wild species of tomato from Peru, the Currant tomato (*L. pimpinellifolium*), is highly resistant to this disease. Its near immunity depends upon a dominant gene *I*. As human food, however, this wild species is of little use, since the fruits are only about a quarter of an inch in diameter and filled with greenish watery pulp and numerous seeds

In 1935, biologists of the U S. Department of Agriculture[1] crossed *L. pimpinellifolium* with an excellent and popular domesticated variety, Marglobe, with the purpose of developing a high-quality tomato that was wilt-resistant. Marglobe has only moderate resistance against the wilt and in infested soil may produce less than half a crop.

The immune F_1 hybrid from the cross Marglobe × *pimpinellifolium* bore fruits about one inch in diameter (Fig. 7) To recover the Marglobe type of fruit and at the same time retain the gene for immunity, the backcross method was used Three backcross generations were obtained In each generation the plants were exposed to the fungus, and only the immune plants (*Ii*) were saved; susceptible plants were discarded

In theory, the first backcross generation should contain on the average three-fourths of its genes from Marglobe More precisely, this is true for those genes in which Marglobe was homozygous The rule is that backcrossing to a homozygous parental type reduces the heterozygosity by ½ in each generation. Hence the second backcross generation should contain on the average ⅞ of the genes of Marglobe. The third generation should have $^{15}/_{16}$ of its genes of the Marglobe type, and so on.

As a result of this backcrossing, all the plants in each backcross generation were necessarily heterozygous for gene *I*, since each backcross brought in gene *i* from Marglobe To get pure-breeding immune plants

[1] W S Porte and F L Wellman, Development of Interspecific Tomato Hybrids of Horticultural Value and Highly Resistant to Fusarium Wilt, *U.S Dept Agr Circ*, 584, 1941

(*II*) the third backcross generation was inbred, and again selection was made for immunity to wilt. After four more generations of inbreeding and selection, a Marglobe type of tomato resulted that was almost 100 per cent immune to wilt. This variety, appropriately named Pan American,

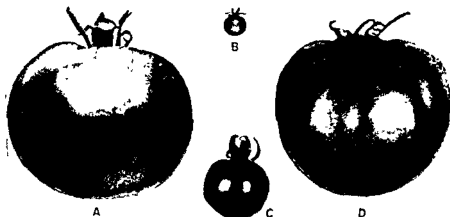


Figure 7. Tomato fruits. (*A*) Marglobe somewhat wilt-resistant parent. (*B*) Currant, highly wilt-resistant parent. (*C*) Highly wilt-resistant F_1 (Marglobe × Currant). (*D*) One of the new highly wilt-resistant Marglobe × Currant hybrids from three generations of backcrossing to Marglobe. (*Photo by Bureau of Plant Industry, Soils, and Agricultural Engineering, U.S. Department of Agriculture.*)

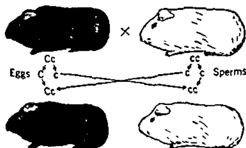


Figure 8. A backcross mating between a hybrid colored guinea pig and a recessive white guinea pig, resulting in a ratio of 1 colored : 1 white.

was released for commercial production in 1941. Its fruit is of good quality, and it ripens somewhat earlier than the original Marglobe. Tomato breeders have used it in crosses with other varieties in order to introduce the gene for immunity into them.

In the development of pure breeds of animals we often wish to know whether a certain individual is hybrid or pure with respect to a dominant character. The backcross method is the simplest and quickest way of finding out. The suspected hybrid, say a colored guinea pig, is mated with a recessive white one, as illustrated in Fig. 8 Since the colored guinea pig represented in the figure is a hybrid, the offspring will appear in the ratio of 1 colored.1 white If the colored animal had been pure, all the offspring would of course have been colored, since colored is dominant Obviously the backcross method of testing is simpler than the method of mating the suspected hybrid to another hybrid, since the ratio from the latter mating would be 3 dominants·1 recessive and, in order to obtain one recessive, would therefore, on the average, necessitate the raising of a larger number of animals than in the backcross mating

THE LAW OF PROBABILITY

Suppose that in testing out a colored guinea pig suspected of being a hybrid, by the backcross method just described, one obtains five offspring, all colored. Does this prove that the colored animal is homozygous? If not, how many colored offspring is it necessary to get before one can say that his animal is homozygous? The answer to these questions is given in the following simple analysis

The prediction of the color of the young guinea pigs is like predicting heads or tails in the fair flip of a coin The causes favoring a sperm with large *C* in fertilizing a given egg are balanced exactly by those favoring a sperm with small *c*, just as the causes in favor of heads are balanced by those in favor of tails What is the chance of obtaining a straight run of five heads? On the first flip the chance of heads is one in two On the second flip the chance is also one in two Therefore the chance of obtaining heads on the first two flips is one-half of one-half, or one in four In like manner the chance of obtaining a run of two black guinea pigs from a hybrid backcrossed to a white is one in four

If there is any doubt in the reader's mind about the last statement, it can be settled by a simple experiment. Let heads stand for black guinea pigs and tails stand for white Toss a coin twice and record the results Repeat 100 times. It will be found that on approximately 25 throws out of 100 there will be a run of two heads, on 25 throws a run of two tails, and on 50 throws one head and one tail, or vice versa.

What is the chance of obtaining a run of three heads, or three black guinea pigs? There has already been a run of two heads in one trial out of four ($\frac{1}{4}$). On the third flip the chance of getting a head is one in two ($\frac{1}{2}$) Therefore in $\frac{1}{2} \times \frac{1}{4}$, or $\frac{1}{8}$, of the times we will get a run of three heads This also can be proved experimentally by tossing three coins.

The rule is now evident. Each time the length of the run is increased by 1 the chance of obtaining it, expressed as a fraction, is divided by 2, as shown in Table 1

If the chance of an event's occurring is one in six (as would be the case in an attempt to throw a given number with a die), the chance of obtaining any two desired numbers, say 2 five spots, with two dice will be $\frac{1}{6} \times \frac{1}{6}$, or one in 36. We can generalize this law of probability a step further by saying that *the chance of two or more wholly independent events occurring simultaneously is equal to the product of the chances of the events occurring separately.*

TABLE 1

Run of 1 head	1 chance in 2
Run of 2 heads	1 chance in 4
Run of 3 heads	1 chance in 8
Run of 4 heads	1 chance in 16
Run of 5 heads	1 chance in 32
Run of 6 heads	1 chance in 64
Run of 7 heads	1 chance in 128
Run of 8 heads	1 chance in 256
Run of 9 heads	1 chance in 512
Run of 10 heads	1 chance in 1,024

Further analysis shows that the same law of probability applies to the relationship among *dependent* events as to that among independent ones For example, suppose one wishes to know his chance of obtaining as the first-born an albino guinea pig from a mating of an albino with a black animal produced by a pair of hybrid blacks, thus·

Hybrid blacks *Cc* × *Cc*

Albino *cc* × Black {*CC* (chance $\frac{1}{3}$) / *Cc* (chance $\frac{2}{3}$)}

What chance of Albino *cc*?

His chance of obtaining an albino depends in the first instance upon the black parent's being heterozygous, since a homozygous black would produce blacks only This chance is $\frac{2}{3}$. In such event he runs a chance of $\frac{1}{2}$ of securing his albino. The probability of the desired result is therefore $\frac{2}{3} \times \frac{1}{2} = \frac{1}{3}$.

An error often made by persons unaccustomed to thinking in terms of probability is in supposing that what has gone before in some mysterious way influences succeeding chances Where there is such an influence we of course are not dealing with chance, since by definition a chance event is one which occurs without an apparent or determinable cause, or as the result of unpredictable forces.

Coming back to our guinea pigs, it is now apparent that from the mating shown in Fig. 8 one should expect once in 32 trials to obtain a run of 5 colored guinea pigs without a single white one, and once in 1,024 trials one should obtain a straight run of 10 colored ones. Under the same rule, once in 1,048,576 times one should obtain 20 colored guinea pigs before obtaining a single white one Experience teaches us that things which can happen only once in 1,000,000 times do happen now and then.

It is evident, therefore, that the question of the purity (homozygosity) of the colored guinea pig becomes a matter of probability The more offspring *the breeder produces without any white ones appearing, the nearer* he approaches certainty that the parent is purebred, or homozygous, but he can never arrive at absolute certainty The point at which the breeder stops his test will depend on practical considerations, such as time and expense involved He may decide after the first 10, all colored, that for his purpose he is reasonably certain of the purity of the animal. Nevertheless, he runs the risk of being wrong once in about a thousand times

To some minds this element of uncertainty in certain problems involving Mendel's laws may appear as a decided weakness, making the application of the laws to man of doubtful value. But such a view has no justification in fact At last analysis, many—if not all—of the so-called laws of nature are statistical laws, i e , laws involving probability. Through reliance on these laws, the affairs of men are conducted with a reasonable degree of success Most of our decisions and activities as individuals are controlled by considerations of probability If men waited for absolute certainty of the success of their enterprises before acting, little would be accomplished.

Since the law of probability is always at work in sexual reproduction, there must be offspring in reasonable numbers before conclusions as to ratios and modes of inheritance can be drawn In a single human family the number of children is usually too small for the observed ratio alone to have great significance For this reason we require many similar consistent pedigrees before we conclude that a given human trait is inherited in accordance with Mendel's laws This is especially true of recessive traits. Albinism, for example, was diagnosed as a recessive single gene difference only upon the basis of numerous consistent pedigrees

As we have seen, the law of probability applies to the occurrence of combinations of primary events as well as to the events themselves Thus in flipping a coin the calculation of the probability of obtaining a run of three heads was found to be $\frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} = \frac{1}{8}$ The run of three is itself an event of a higher order than the flip of a single coin

Suppose we wish to know the chance of obtaining any particular combination of heads and tails, such as two heads and one tail in three flips We may find the answer by writing down all the possible runs and noting

what fraction of the total consists of two heads and one tail. The following eight runs alone are possible, and each is equally likely of occurrence

1st flip	*2d flip*	*3d flip*	*Run*		
head ½	head ½	head ½	⅛		3 heads 0 tail
head ½	head ½	tail ½	⅛		
head ½	tail ½	head ½	⅛	⅜	2 heads 1 tail
tail ½	head ½	head ½	⅛		
tail ½	tail ½	head ½	⅛		
tail ½	head ½	tail ½	⅛	⅜	2 tails: 1 head
head ½	tail ½	tail ½	⅛		
tail ½	tail ½	tail ½	⅛		3 tails 0 head

We were interested merely in the chance of obtaining the combination 2 heads and 1 tail and not in the order in which heads and tails came up. Evidently three of the runs out of eight are of this constitution, and the answer to our problem is three times in eight

A much shorter method for obtaining an answer to our question is the use of the binomial theorem To illustrate, let x = the chance of obtaining heads (½) and y the chance of obtaining tails (½). The binomial $(x + y)$ is raised to the power corresponding to the total number of individuals or events—in this case, 3 Hence in our problem we expand $(x + y)^3 = x^3 + 3x^2y + 3xy^2 + y^3$ The first term (x^3) represents the chance of obtaining 3 heads, the second term $(3x^2y)$, the chance of 2 heads and 1 tail; the third term $(3xy^2)$, the chance of 1 head and 2 tails; and the last term (y^3), the chance of 3 tails Substituting ½ for x and ½ for y, we obtain for the second term $3 \cdot ½ \cdot ½ \cdot ½ = ⅜$, the chance of 2 heads and 1 tail

The binomial theorem may also be used where the values of x and y are unequal For example, suppose that we wish to know the chance of obtaining two albino and two black guinea pigs as the first four offspring of a mating of two heterozygotes (*Cc* × *Cc*). Let x = the chance of a black guinea pig (¾) and y the chance of an albino (¼). Expanding the binomial $(x + y)^4$, we get $x^4 + 4x^3y + 6x^2y^2 + 4xy^3 + y^4$. Substituting in the appropriate term $(6x^2y^2)$ we have $6 \cdot ¾ \cdot ¾ \cdot ¼ \cdot ¼ = 27/128$ (approximately ⅕).

A short cut that saves us writing out the entire expansion will now be given. Suppose our problem is to calculate the chance of obtaining 12 black and 5 albino guinea pigs from a backcross mating (*Cc* × *cc*). Instead of expanding $(x + y)^{17}$ in full we merely apply the rule for obtaining the coefficient of the single term, as follows:

$$\frac{17 \cdot 16 \cdot 15 \cdot 14 \cdot 13}{1 \cdot 2 \cdot 3 \cdot 4 \cdot 5} = 6{,}188x^{12}y^5$$

The rule for finding the coefficient of the term desired is perhaps obvious

from the above example: the numerator of the compound fraction is $n(n-1)(n-2)\ .\ .\ .$, etc, the last factor being one more than the exponent of x. The denominator is $1 \cdot 2\ 3 \cdot \cdot \cdot \cdot$, etc, the last factor being the same as the exponent of y

Now, substituting ½ for x and ½ for y, we obtain

$$6{,}188\ \ (\tfrac{1}{2})^{12}\ \ (\tfrac{1}{2})^{6} = \frac{6{,}188}{131{,}072} = \frac{1}{21}$$

approximately; this is the chance of obtaining a ratio of 12 5 where a ratio of 1.1 is expected

Where small numbers of individuals only are involved, the use of the binomial theorem is of great practical value in giving the probability of obtaining by chance a particular ratio among two classes of individuals For larger numbers and for problems dealing with more than two classes of individuals, other statistical methods have been developed One of these is described in the next chapter

ANALYSIS OF PEDIGREES

In human heredity two questions often arise. (1) Does a given characteristic follow Mendel's laws? (2) What are the probabilities that a given Mendelian characteristic will appear in the offspring of a particular mating?

In attempting to answer the first question with respect to man, Mendel's technique of controlled breeding experiments obviously is not practicable. We must study the pedigrees of human families as we find them. For example, take the case of albinism in man In albinism there is almost total lack of pigment in the skin, hair, and eyes. The eyes appear pink as a result of the reflection of light from the blood vessels of the eye. The vision is very defective, not only because of the extreme sensitiveness to light (note squinting of albino child in Fig. 9), but also because of the imperfect development of the retina itself. The skin of albinos also appears pink where the blood vessels approach the surface Albinos occur in all races of man, except perhaps in the Australian Aborigines, and probably in all species of domesticated mammals, as well as in wild species. Practically every large museum of natural history displays mounted specimens of albinos representing various wild species, such as woodchucks, porcupines, skunks, opossums, squirrels, etc

In laboratory mammals such as white mice, white rats, white rabbits, white guinea pigs, and so on, albinism is invariably inherited as a recessive It is, therefore, probably inherited in the same manner in wild animals In man, a study of hundreds of pedigrees points to the same con-



Figure 9. An albino boy and his normally pigmented twin, offspring of normally pigmented Mexican parents. The eyes of the albino have a pinkish cast. Three other children in the same family are normal. (*From Windle, J. Heredity, January,* 1935.)

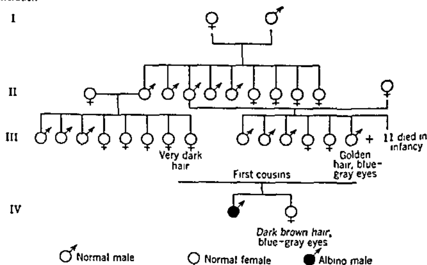


Figure 10. Pedigree showing an albino boy born to normal parents who are first cousins. (*From Pearson, Nettleship, and Usher, "A Monograph on Albinism in Man," part 4, Dulau & Co., London,* 1913.)

clusion. When both parents are albinos, the children are all albinos[1] Most human albinos, however, as in wild-animal species, come from normally pigmented parents (Fig. 9). This is true whether the parents are Caucasians, Negroes, or Mongolians. The occurrence of an albino under such circumstances depends upon the chance mating of two individuals both heterozygous with respect to the albino gene. A typical pedigree taken from an extensive monograph on albinism is shown in Fig 10 In this pedigree the gene for albinism probably had been carried for a good many generations without making its presence known. The marriage of cousins merely increased the chance that each parent would carry the gene The monograph also includes many pedigrees showing albino children from marriages of unrelated persons[2] From all the evidence at hand, we are justified in concluding that albinism in man, like that in other mammals, is a recessive character.

Knowing that a given human trait is Mendelian, its appearance in the offspring can be predicted with the same degree of certainty as in other organisms For example, one might ask, what is the chance that a mating of two normal persons, each with an albino brother or sister, would produce an albino child? Since the parents of the pigmented child shown in Fig. 9 must both be heterozygous for albinism, the child himself has a chance of one in three of being entirely free from the gene for that character. This leaves two chances out of three that he is heterozygous for the gene. If later he should marry a woman who also had an albino brother or sister (she like himself would have a chance of two in three of being heterozygous for the albino gene), the chances of both partners in marriage being simultaneously heterozygous for the albino gene would be $2/3 \times 2/3 = 4/9$ (four out of nine) If both parents should happen to be heterozygous for the albino gene, the chance of the first child being an albino would of course be one in four. Multiplying one of these probabilities by the other, in accordance with the law of probability heretofore stated, we can say that the chance of an albino as the first child of two normally pigmented persons, both from families in which there is an albino brother or sister, is $4/9 \times 1/4 = 1/9$ (one in nine) The same rule holds, of course, for any recessive trait. Therefore, where questionable genes are concerned, it becomes plainly a matter in which the prospective partners in marriage may decide for themselves whether the risk of an undesirable recessive character appearing in their children is too great to be run

[1] A few exceptional cases have been reported If authentic, these are possibly the result of a mutation of the albino gene back to normal Such reverse mutations are occasionally observed in Drosophila

[2] For a discussion of the relationship of cousin marriages to the expression of recessive traits, see Chap 13

Mutations affecting pigmentation probably occur in all mammals. In April, 1955, a young white spider monkey with blue eyes (Fig. 11) was shipped to the Chicago Zoological Park from Florida. Blue-eyed mutants



Figure 11. Young white spider monkey with blue eyes —so far as known the first case of its kind on record. (*Courtesy of Chicago Zoological Park and Chicago Daily Tribune*)

are found in cats and horses This seems to be the first recorded case of a blue-eyed primate, other than man.

LACK OF DOMINANCE—HYBRID INTERMEDIATE

Mendel chose for his final experiments pairs of contrasting characters in which essentially complete dominance of one character prevailed over the other. He observed, however, that dominance was not a universal law in peas. In his preliminary experiments he discovered that certain characters did not permit a sharp and certain separation, since the difference was of a "more or less" nature often difficult to define. The length of flower stalk was one such character in which dominance was

not complete. On the whole, it gave a fairly satisfactory result, although he could not distinguish and classify with certainty all the individuals

Another character in which there was a lack of dominance was that of flowering time When he crossed varieties which differed by at least 20 days from the middle of the flowering period of one to that of the other, he found that the flowering time of the hybrid was almost exactly half-way between those of the egg and pollen parents While he did not carry this experiment through to the end, he concluded that the breeding behavior of the hybrids with respect to this character probably followed the law ascertained in the case of completely dominant characters.

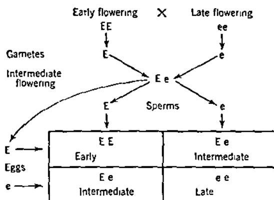


Figure 12. Diagram showing a 1:2:1 ratio among the offspring from hybrids in a case of lack of dominance (1 early 2 intermediate· 1 late).

The diagram illustrating the distribution of the genes in the above case (Fig. 12) is obviously identical with the diagram for complete dominance (page 13). The difference in the two cases lies entirely in the expression of the contrasting characters of the hybrids: here the hybrid is intermediate, and therefore distinguishable from both parents The observable ratio among the offspring of the hybrids is therefore 1.2:1 instead of 3:1.

The difference between cases of dominance and lack of dominance evidently relates to the physiological effect of the genes in the hybrid. Where dominance exists a single dose of the dominant gene produces the same effect as a double dose, while in lack of dominance the two genes cooperate in development to produce a character in the hybrid more or less intermediate between the two original characters The expression incomplete dominance, or partial dominance, is sometimes used to cover cases such as the one described, especially where the hybrids tend to resemble one parent much more than the other.

During the years since the rediscovery of Mendel's laws, many cases of lack of dominance or incomplete dominance have been discovered in plants and animals, as well as in man In all such cases, Mendel's conclusion *that the law of segregation applies just as in the case of dominance* has been fully confirmed.

Examples of Lack of Dominance in Man

Hair Form. The form of the hair, with reference to curly and straight as found in Caucasians of European descent, illustrates a Mendelian trait showing lack of dominance. The hybrid is intermediate, having wavy hair The extent of waviness is variable, however, and some hybrids may be classed as curly-haired. Curly hair, therefore, is sometimes called an incomplete dominant

Two straight-haired parents have only straight-haired children, and two purebred curly-haired parents have only curly-haired children; but to avoid mistakes in classification it should be remembered that wavy hair has a tendency to straighten out with advancing age, and that a wavy-haired person may appear straight-haired if the hair is cut short.

A marriage between a straight-haired person and a wavy-haired person results in children with straight hair and wavy hair in the ratio of 1 1. Actual figures for such matings, as cited by Cockayne,[1] are straight hair 61 wavy hair 52. This author also gives figures for children, both of whose parents had wavy hair, as follows: 27 straight:51 wavy:22 curly. This ratio is very close to 1.2.1 and therefore agrees with what we should expect from hybrids where dominance is lacking.

The inheritance of hair form in the Negroid and Mongoloid divisions of mankind does not follow this simple plan. Its consideration, therefore, is deferred to a later chapter.

Thalassemia. There are two types of the blood disease thalassemia (*thalassa*, sea; *anemia*, want of blood)—thalassemia major and thalassemia minor The former, now known to be the homozygote (*MM*), is a fatal disease of childhood It is found almost exclusively in peoples of Mediterranean stock Numerous studies have been made in Italy and in this country among people of Italian ancestry The symptoms of the disease include enlarged spleen, anemia, and changes in the bones and pigment of the viscera and skin Also called Cooley's anemia, thalassemia major was first described in detail by two Detroit physicians, Cooley and Lee,[2] in 1925

In 1925 an Italian physician described a milder nonfatal form of the

[1] E A. Cockayne, "Inherited Abnormalities of the Skin and Its Appendages," Oxford University Press, London, 1933

[2] T B Cooley and P. Lee, Series of Cases of Splenomegaly in Children with Anemia and Peculiar Bone Changes, *Trans Am Pediat Soc*, 37:29-30, 1925



Figure 13. Approximate distribution of thalassemia minor in Italy. Frequency progressively higher in the more heavily shaded areas. (*From Bianco et al., Ann. Eugenics,* 16:308, 1952.)

disease, now known as thalassemia minor. This has been shown to be the heterozygote (*Mm*) The minor form is characterized by enlarged spleen and mild anemia, with red corpuscles of reduced size but above normal in numbers. Several different blood tests make diagnosis relatively certain. No cure for either form of thalassemia has been found. Neel[1] has

[1] J. V. Neel, The Population Genetics of Two Inherited Blood Dyscrasias in Man, *Cold Spring Harbor Symposia Quant. Biol*, 15:141–158, 1950

given a summary of the numerous clinical and genetic studies of the disease, with citations of articles

Italian investigators[1] have found that the heterozygote (*Mm*) gives rise to various phenotypes, ranging from healthy to rather severely anemic and jaundiced individuals They suggest that this variability in expression of the gene *M* in heterozygotes is due to the interplay of modifying genes They also find that the frequency of thalassemia minor in Italy varies from about 0 5 per cent in most of the country to about 10 0 per cent in the district of Ferrara (Fig 13) They have not yet found a satisfactory explanation for this variation in frequency.

PROBLEMS

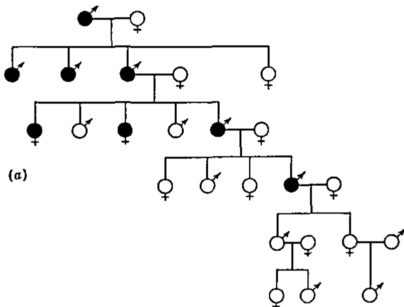
1. In the plant known as the four-o'clock, there is lack of dominance between the flower colors red (*RR*) and white (*rr*) The hybrid (*Rr*) is pink Give the ratios of the colors expected from the following cross-pollinations
   a Red × pink
   b Pink × white
   c Pink × pink
   d List the other possible matings of four-o'clocks of the above three varieties
2. In peas, tall (*TT*) is dominant over short (*tt*) Four experiments in cross-pollination gave the results shown below In each case give the most probable gene formula of the parents, as indicated by the ratio among their offspring:
   a Tall × tall produced 95 tall, 29 short
   b Tall × short produced 50 tall, 0 short
   c. Tall × tall produced 75 tall, 0 short
   d Tall × short produced 8 tall, 4 short.
3. Starting with a hybrid (F_1) from two pure varieties of peas, round (*RR*) and wrinkled (*rr*), find the percentage of hybrids in each of the next four generations (F_2, F_3, F_4, and F_5) resulting from self-fertilization of all individuals in each generation (Assume that all individuals are equally productive)
4. List in chronological order the steps that were taken by plant breeders in developing the Pan American variety of tomatoes Give the reasons for each step
5. Assume that one person out of 70 in the population as a whole is heterozygous (carrier) with respect to the recessive gene for albinism (according to calculations this is somewhere near the actual figure) Assume also that marriages are purely at random with respect to persons who are carriers (*Aa*) and those who are not (*AA*). Disregarding marriages of albinos, what is the expected proportion of all births that are albinos?
6. A normal person, whose parents are normal, has a grandparent who is an albino Assume that all the other grandparents are free from the gene for albinism What is the chance that this person is a carrier of the albino gene?
7. If the person mentioned in Problem 6 marries an individual with a similar pedigree, what chance is there that their first child will be an albino?

[1] I. Bianco, G Montalenti, E Silvestroni, and M. Siniscalco, Further Data on Genetics of Microcythaemia or Thalassaemia Minor and Cooley's Disease or Thalassaemia Major, *Ann. Eugenics*, 16:299–315, 1952.

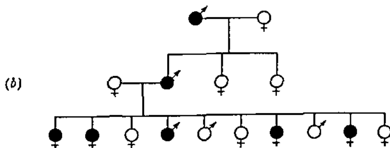
8 A normal person, whose parents are normal, has a grandparent who carries the gene for albinism Assume that all the other grandparents are free from the gene for albinism. What is the chance that this person is a carrier of the albino gene?

9. Explain the fact that defective traits due to dominant genes are more easily eliminated from a population than are defective traits due to recessive genes

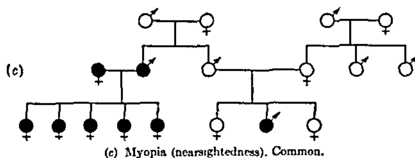
10. In the following human pedigrees the characteristic mentioned beneath the pedigree is indicated by a solid black circle The normal condition is indicated by an open circle Assume for each trait that the difference between the normal and the affected individuals is due to a single gene difference, as in albinism Determine in each case whether the characteristic is recessive or probably dominant Some of the characteristics are very rare The others are found in a small minority of the population



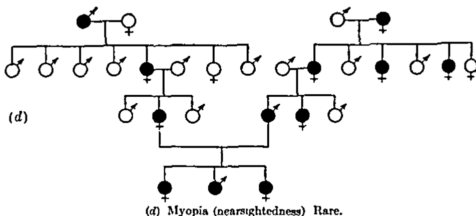
(a) Pick's disease (atrophy of the brain) Very rare



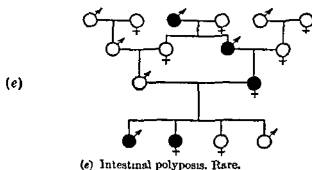
(b) Aniridia (absence of the iris). Very rare



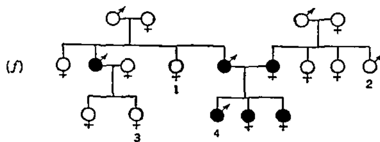
(c) Myopia (nearsightedness). Common.

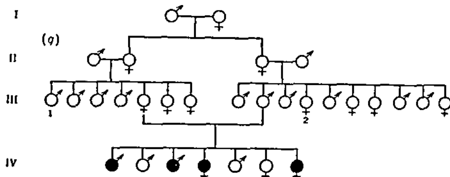


(d) Myopia (nearsightedness) Rare.



(e) Intestinal polyposis. Rare.





(g) Spastic paraplegia (paralysis of the legs) Very rare

11. In a marriage between individuals 1 and 2 in the pedigree for deafness (*f*), what is the chance of the first child's being deaf? What is the chance of a deaf child from a marriage between 3 and 4?

12. In a marriage between individuals 1 and 2 in the pedigree for spastic paraplegia (*g*), what is the chance that the first child will develop the disease? (Assume that the mothers of 1 and 2 are both carriers of the gene and that their fathers are both free from it) What is the chance that one of the normal children in generation IV is a carrier of the gene?

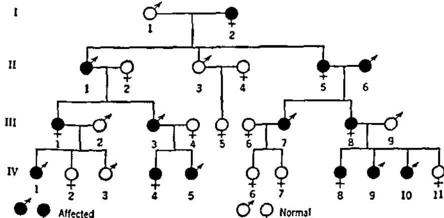
13. Give two possible explanations for the fact that in human beings it is much easier to discover pedigrees of dominant characteristics than pedigrees of recessive characteristics

14. From a mating of two wavy-haired persons what is the chance that the first four children will be straight-haired?

15. In a mating between a wavy-haired person and a straight-haired mate what is the chance that the first child will be straight-haired and the next three wavy-haired?

16. Calculate by means of the binomial theorem the chance that in the mating mentioned in Problem 15 two of the four children will be straight-haired and two wavy-haired

17. Toss four coins simultaneously for 32 throws and record at each throw the combination of heads and tails Record the resulting ratio of combinations obtained, and hand this in so that your result may be compared with the combined ratio obtained by the class as a whole



18 In the pedigree of a dominant trait shown at the bottom of page 35, give the genotypes of the following individuals, using the symbol *D* for dominant and *d* for recessive I-2, II-2, II-3, II-5, II-6, III-8, IV-3, IV-8

19. In the pedigree above what is the probability that

a. A third child from II-5 × II-6 will be affected?

b. A third child from III-3 × III-4 will be affected?

c A third child from III-6 × III-7 will be affected?

d From a marriage of IV-1 × IV-11 the first three children will be unaffected?

e From a marriage of IV-3 × IV-4 two of the first four children will be affected and two unaffected?

f From a marriage of IV-5 × IV-8 two will be affected and two unaffected among the first four children?

20 In corn, a recessive gene known as albino (*aa*) prevents the formation of chlorophyll in the leaves and stem Being unable to synthesize its own food, after reaching a few inches in height an albino plant dies of starvation Corn is normally cross-pollinated, but may be readily self-pollinated by hand Given an ear of corn guaranteed to produce a ratio of three green plants to one albino (1 *AA*, 2 *Aa*, 1 *aa*), write out a list of numbered steps, in chronological order, that you would follow in producing another ear of the same type

3

DIHYBRIDS: THE LAW OF INDEPENDENT ASSORTMENT

The discovery of the law of heredity just described (the law of segregation) was no small accomplishment, but Mendel did not stop at that point. He recognized that a complex organism contains many determiners (genes) and that if we are to gain an understanding of the organism as a whole, we must be able to put two or more pairs of genes together and interpret the results His solution of this problem proved to be as brilliant as that of the simpler one. Let us now examine the method of solution of the more complex problem.

Using the seven pairs of contrasting characters previously mentioned, Mendel had found that the dominant and the recessive in each pair were as follows:

	Dominant		*Recessive*	
1	Round seeds	(*RR*)	Wrinkled seeds	(*rr*)
2.	Yellow cotyledons	(*YY*)	Green cotyledons	(*yy*)
3	Gray-brown seed coats and violet-red flowers	(*BB*)	White seed coats and white flowers	(*bb*)
4	Inflated pods	(*II*)	Constricted pods	(*ii*)
5	Green unripe pods	(*GG*)	Yellow unripe pods	(*gg*)
6	Axial flowers	(*AA*)	Terminal flowers	(*aa*)
7	Tall plant	(*TT*)	Dwarf plant	(*tt*)

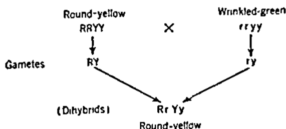
By a series of carefully planned experiments he demonstrated that these characters could be sorted out and recombined in the same free manner as though they were cards shuffled and dealt by a player. One of his experiments, which is typical in its methods and results, is described below.

A DIHYBRID MATING

Mendel crossed a variety combining the seed characters round and yellow with a variety combining the characters wrinkled and green He does not tell us how he obtained the two pure varieties, but since the

shape of peas is commonly either round or wrinkled and the color either yellow or green, he may have been able to select two which suited his purpose from his 22 varieties He could have produced them easily by making the proper crosses

The hybrid offspring from this cross were all round yellow, as shown below·



Mendel planted the dihybrids and obtained from them as a result of self-fertilization four sorts of seeds, the actual numbers of which were as follows

Dihybrids (*RrYy*)
↓
(9) 315 Round and Yellow
(3) 101 Wrinkled and Yellow
(3) 108 Round and Green
(1) 32 Wrinkled and Green

Frequently all four sorts were in the same seed pod. It is obvious that the ratio of the four kinds is almost a perfect 9 3 3:1.

Mendel's explanation of this result, which proved to be entirely correct, is based upon the assumption that there is a separate gene for each character, that the genes occur in pairs in the cells of the plant; that each gamete receives only one member of each pair of genes; that as many kinds of gametes are formed, in equal numbers, as there are possible combinations of genes; and finally, that all four kinds of sperms have an equal opportunity of fertilizing the four kinds of eggs.

These various assumptions are all represented diagrammatically in Fig. 14. The combinations of the eggs and sperms at fertilization are merely an application of the law of probability previously considered. For example, since one-fourth of all the eggs carry *ry* and one-fourth of the sperms carry *ry*, the chance of a union between the two (*rryy*) is $\frac{1}{4} \times \frac{1}{4}$, or $\frac{1}{16}$ (one in 16); because, as previously explained, the chance of the simultaneous occurrence of two independent events is equal to the product of their chances of occurring separately

In the same way, the chance of any other one of the 16 possible com-

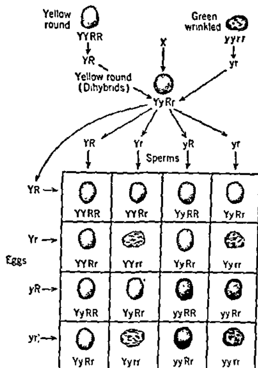


Figure 14. Diagram showing Mendel's results from crossing two varieties of peas differing in two independent characteristics. The offspring of the dihybrids are represented in the squares of the checkerboard in their actual numerical ratios: 9 yellow round 3 yellow wrinkled 3 green round: 1 green wrinkled

binations taking place is $\frac{1}{4} \times \frac{1}{4}$, or $\frac{1}{16}$ (one in 16) Each of these combinations is represented by a square on the checkerboard

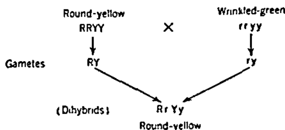
The Fractional Method of Calculating Ratios

The advantage of the checkerboard method of calculating Mendelian ratios, introduced by the British geneticist R. C. Punnett, is that it shows graphically each essential step. the formation of the gametes, their union to form zygotes, and the resulting phenotypes Its disadvantage is that it is time-consuming and offers many opportunities for making clerical errors Many persons, therefore, prefer an algebraic method, or a fractional method, such as the one illustrated below A detailed description of the fractional method has been published by Jones [1]

[1] M D Jones, The Fractional Method of Analysis of Factors: An Aid in Teaching Genetics, *J. Heredity*, 38:368-370, 1947

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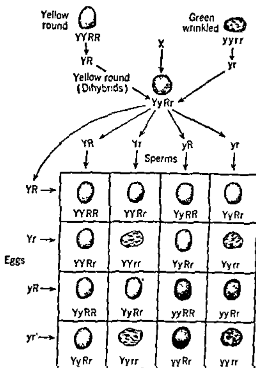


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F_1 Dihybrid *RrYy*
F_2 Phenotypes (using roman letters for characters)

$\frac{3}{4}$ R $\frac{3}{4}$ Y = $\frac{9}{16}$ Round Yellow
$\frac{1}{4}$ r $\frac{3}{4}$ Y = $\frac{3}{16}$ Wrinkled Yellow
$\frac{3}{4}$ R · $\frac{1}{4}$ y = $\frac{3}{16}$ Round Green
$\frac{1}{4}$ r · $\frac{1}{4}$ y = $\frac{1}{16}$ Wrinkled Green

This method may be used in calculating genotypic ratios by splitting the dominants into homozygotes and heterozygotes, thus:

F_1 Dihybrid *RrYy*

F_2 Genotypes			F_2 Phenotypes
$\frac{1}{4}$ *RR*	$\frac{1}{4}$ *YY*	= $\frac{1}{16}$ *RRYY*	$\frac{9}{16}$ Round Yellow
$\frac{1}{4}$ *RR*	$\frac{1}{2}$ *Yy*	= $\frac{2}{16}$ *RRYy*	
$\frac{1}{2}$ *Rr*	$\frac{1}{4}$ *YY*	= $\frac{2}{16}$ *RrYY*	
$\frac{1}{2}$ *Rr*	$\frac{1}{2}$ *Yy*	= $\frac{4}{16}$ *RrYy*	
$\frac{1}{4}$ *rr*	$\frac{1}{4}$ *YY*	= $\frac{1}{16}$ *rrYY*	$\frac{3}{16}$ Wrinkled Yellow
$\frac{1}{4}$ *rr*	$\frac{1}{2}$ *Yy*	= $\frac{2}{16}$ *rrYy*	
$\frac{1}{4}$ *RR*	$\frac{1}{4}$ *yy*	= $\frac{1}{16}$ *RRyy*	$\frac{3}{16}$ Round Green
$\frac{1}{2}$ *Rr*	$\frac{1}{4}$ *yy*	= $\frac{2}{16}$ *Rryy*	
$\frac{1}{4}$ *rr*	· $\frac{1}{4}$ *yy*	= $\frac{1}{16}$ *rryy*	$\frac{1}{16}$ Wrinkled Green

Testing the Offspring of the Dihybrids

The rule just disclosed was of far-reaching importance if it could be proved to be of general application, since it showed that an organism was like a mosaic, consisting of many characters, and that by the proper matings the various characters could be sorted out and recombined at will

In order to establish this principle beyond doubt, Mendel went to great trouble. The following year he planted all 556 seeds obtained from the dihybrids With painstaking care he tells us exactly how many seeds of each group either failed to develop or did not produce seeds. Altogether there were only 27 nonproductive seeds The remaining 529 seeds proved by the progeny which they produced that they belonged to the following nine genetic types (*genotypes*):

RrYy	(Round Yellow)	138	301	(9)
RRYy	(Round Yellow)	65		
RrYY	(Round Yellow)	60		
RRYY	(Round Yellow)	38		
Rryy	(Round Green)	67	102	(3)
RRyy	(Round Green)	35		

rrYy	(Wrinkled Yellow)	68	96	(3)
rrYY	(Wrinkled Yellow)	28		
rryy	(Wrinkled Green)	30	30	(1)

An inspection of the checkerboard (Fig 14) shows that theoretically these nine genotypes are expected in the same ratio as found by Mendel

Obviously the round yellow peas are of four genotypes, while the round green peas and wrinkled yellow peas are each of two genotypes There is only one type of wrinkled green, since this is the double recessive.

In addition to the foregoing experiment, Mendel performed others in which he united the remaining characters by two's as hybrids and in all cases obtained the same results

On the basis of these several experiments it is now possible to predict that dihybrids will produce nine genetically different types of offspring and that these will appear in the definite ratio indicated above If dominance is complete for both pairs of characters, these nine genotypes will group themselves under four visible types (*phenotypes*) in the ratio of 9:3:3:1. The law illustrated by the experiment just described is known as the *law of independent assortment.*

LACK OF DOMINANCE IN DIHYBRIDS

In all of Mendel's experiments with dihybrids, dominance was present. The law of independent assortment holds good, however, whether there is dominance or not, just as does the law of segregation It should be emphasized that dominance relates to the *physiological effects* of genes, while the law of independent assortment concerns the *distribution* of the genes.

To illustrate independent assortment without dominance we may choose a well-known case in cattle. In hair color, red is due to a pair of genes, *RR*. White may be designated *rr*. The hybrid, *Rr*, is not red but roan (red hairs intermingled with white hairs). The three colors red, roan, and white are all found in the shorthorn breed of cattle (Fig 15) Roans are highly prized by cattle breeders Unfortunately, since roans are always heterozygous they never breed true: when two roans are mated they yield reds, roans, and whites in the ratio of 1.2·1. It is of course possible to obtain pure-breeding races of reds and whites simply by mating them with their own color exclusively.

Hereditary lack of horns (known as polled) is due to a simple dominant gene, *H*. Horns are due to a recessive, *h* Among the shorthorns there are hornless as well as horned animals (Fig 15). Since the character *horns* is independent of color it is easy to produce pure races of reds or whites, with or without horns, as desired.

F_1 Dihybrid *RrYy*
F_2 Phenotypes (using roman letters for characters)

$\frac{3}{4}$ R · $\frac{3}{4}$ Y = $\frac{9}{16}$ Round Yellow
$\frac{1}{4}$ r · $\frac{3}{4}$ Y = $\frac{3}{16}$ Wrinkled Yellow
$\frac{3}{4}$ R · $\frac{1}{4}$ y = $\frac{3}{16}$ Round Green
$\frac{1}{4}$ r · $\frac{1}{4}$ y = $\frac{1}{16}$ Wrinkled Green

This method may be used in calculating genotypic ratios by splitting the dominants into homozygotes and heterozygotes, thus:

F_1 Dihybrid *RrYy*

F_2 Genotypes	F_2 Phenotypes
$\frac{1}{4}$ *RR* · $\frac{1}{4}$ *YY* = $\frac{1}{16}$ *RRYY*	$\frac{9}{16}$ Round Yellow
$\frac{1}{4}$ *RR* · $\frac{1}{2}$ *Yy* = $\frac{2}{16}$ *RRYy*	
$\frac{1}{2}$ *Rr* · $\frac{1}{4}$ *YY* = $\frac{2}{16}$ *RrYY*	
$\frac{1}{2}$ *Rr* · $\frac{1}{2}$ *Yy* = $\frac{4}{16}$ *RrYy*	
$\frac{1}{4}$ *rr* · $\frac{1}{4}$ *YY* = $\frac{1}{16}$ *rrYY*	$\frac{3}{16}$ Wrinkled Yellow
$\frac{1}{4}$ *rr* · $\frac{1}{2}$ *Yy* = $\frac{2}{16}$ *rrYy*	
$\frac{1}{4}$ *RR* · $\frac{1}{4}$ *yy* = $\frac{1}{16}$ *RRyy*	$\frac{3}{16}$ Round Green
$\frac{1}{2}$ *Rr* · $\frac{1}{4}$ *yy* = $\frac{2}{16}$ *Rryy*	
$\frac{1}{4}$ *rr* · $\frac{1}{4}$ *yy* = $\frac{1}{16}$ *rryy*	$\frac{1}{16}$ Wrinkled Green

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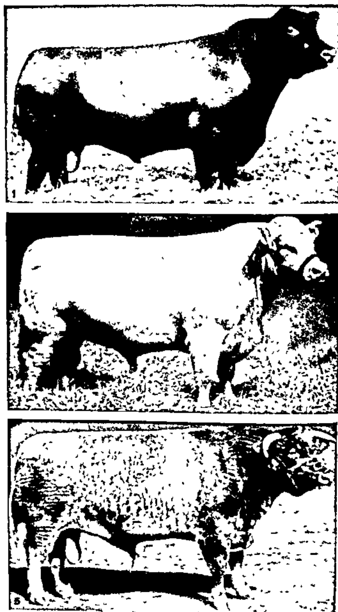


Figure 15 Prize shorthorn cattle (1) Red polled bull (3) White polled bull (5) Roan horned bull (1 *and* 3 *from photographs by Robert F Hildebrand,* 5 *from a photograph by H A Strohmeyer, Jr. Courtesy of Encyclopaedia Britannica, U S. ed., vol* 5, *plate* 1, *at p.* 48, 1945.)

If a mating is made between a red hornless animal and a white horned animal, the offspring will all be roan hornless, regardless of which one is the male and which the female, as follows.

Red-hornless RRHH × White-horned rrhh

Gametes: RH, rh

(Dihybrids) Rr Hh Roan-hornless

If two of these roan hornless hybrids are mated, the offspring are as shown in Fig 16

Roan-hornless Rr Hh × Roan-hornless Rr Hh

Eggs \ Sperms	RH	Rh	rH	rh
RH	RRHH Red hornless	RRHh Red hornless	RrHH Roan hornless	RrHh Roan hornless
Rh	RRHh Red hornless	RRhh Red horned	RrHh Roan hornless	Rrhh Roan horned
rH	RrHH Roan hornless	RrHh Roan hornless	rrHH White hornless	rrHh White hornless
rh	RrHh Roan hornless	Rrhh Roan horned	rrHh White hornless	rrhh White horned

Figure 16. Diagram showing the results of mating two roan cattle, each of which is hybrid with respect to hornless. The visible ratio is 3 red hornless 6 roan hornless· 3 white hornless 1 red horned 2 roan horned 1 white horned

The number of visible types (phenotypes) here obtained is six instead of four as it would have been with dominance in both pairs of genes The number of genotypes, however, remains the same, i.e., nine. If dominance had been lacking with respect to horns as well as color, the number of

visible types would have been increased to nine and there would then have been the same number of phenotypes as genotypes.

The fractional method may also be used in problems where there is lack of dominance, for example, in the cattle problem, just worked with the checkerboard, we have:

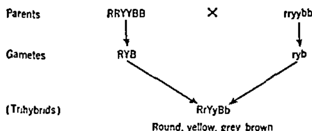
F_1 Dihybrids *RrHh*

F_2 Phenotypes (using roman letters for characters)

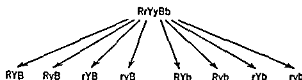
$\frac{1}{4}$ R	$\frac{3}{4}$ H	= $\frac{3}{16}$ R H		(Red Hornless)
$\frac{1}{2}$ Rr	$\frac{3}{4}$ H	= $\frac{6}{16}$ Rr H		(Roan Hornless)
$\frac{1}{4}$ r	$\frac{3}{4}$ H	= $\frac{3}{16}$ r H		(White Hornless)
$\frac{1}{4}$ R	$\frac{1}{4}$ h	= $\frac{1}{16}$ R h		(Red Horned)
$\frac{1}{2}$ Rr	$\frac{1}{4}$ h	= $\frac{2}{16}$ Rr h		(Roan Horned)
$\frac{1}{4}$ r	$\frac{1}{4}$ h	= $\frac{1}{16}$ r h		(White Horned)

TRIHYBRIDS SHOW INDEPENDENT ASSORTMENT

Having demonstrated the law of independent assortment for two pairs of characters, Mendel next performed an experiment in precisely the same manner except that he used three pairs of characters. Of all his experiments he states that this one demanded the most time and trouble The cross is represented as follows.



Mendel planted all the seeds which he obtained from the trihybrids and found that each of the three characters segregated independently of the other two characters The principle governing trihybrids was found to be identical with the principle governing dihybrids. It is easy to see why this should be so if we look for a moment at the constitution of the trihybrids. Since they are hybrid in three separate respects, they will produce gametes of the following eight types:



Note that the combinations on the left are identical with those on the right except that those on the left have a large *B* instead of a small *b*. The

addition of a third pair of genes has obviously doubled the number of possible combinations

The union at fertilization of eight kinds of eggs with eight corresponding kinds of sperms, in a purely fortuitous manner, produces a population consisting of 27 different genotypes instead of the 9 genotypes produced by dihybrids In order to work out this problem in detail by the checkerboard method as we did for the dihybrid (Fig 14) we would need to use a checkerboard having eight squares each way instead of four This would be very time-consuming With three or more pairs of genes the fractional method is shorter and the chance of error is reduced To illustrate with the above trihybrid:

F_1 Trihybrid *RrYyBb*

F_2 Phenotypes (using roman letters for characters)

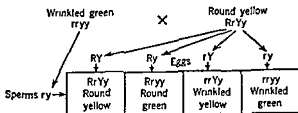
$\frac{3}{4}$ R $\frac{3}{4}$ Y $\frac{3}{4}$ B = $\frac{27}{64}$ R Y B
$\frac{3}{4}$ R $\frac{1}{4}$ y $\frac{3}{4}$ B = $\frac{9}{64}$ R y B
$\frac{1}{4}$ r $\frac{3}{4}$ Y $\frac{3}{4}$ B = $\frac{9}{64}$ r Y B
$\frac{1}{4}$ r $\frac{1}{4}$ y $\frac{3}{4}$ B = $\frac{3}{64}$ r y B
$\frac{3}{4}$ R $\frac{3}{4}$ Y $\frac{1}{4}$ b = $\frac{9}{64}$ R Y b
$\frac{3}{4}$ R $\frac{1}{4}$ y $\frac{1}{4}$ b = $\frac{3}{64}$ R y b
$\frac{1}{4}$ r $\frac{3}{4}$ Y $\frac{1}{4}$ b = $\frac{3}{64}$ r Y b
$\frac{1}{4}$ r $\frac{1}{4}$ y $\frac{1}{4}$ b = $\frac{1}{64}$ r y b

In cases of complete dominance, the 27 different genotypes from trihybrids fall into 8 visibly different types as compared with the 9 genotypes and 4 visibly distinct types obtained from dihybrids

On a smaller scale Mendel performed similar experiments, combining other characters by two's and three's, until he had convinced himself that all seven of the characters chosen for study in his experiments followed the same law; that is, that each of the characters was independent of the other characters All possible constant combinations of the seven differentiating characters (128 combinations in all) were actually obtained by Mendel through repeated crossing This, also, must have involved a great amount of labor.

BACKCROSSING DIHYBRIDS

As a final test of his theory of independent assortment, Mendel performed a backcross experiment using one of his dihybrids and the double recessive as follows.



Mendel reasoned that if his theory was correct, the dihybrid should form four kinds of eggs as shown above The double recessive should form but one kind of sperm (*ry*) If all four kinds of eggs are produced in equal numbers, there should result at fertilization four kinds of offspring in equal numbers: ¼ round yellow, ¼ round green, ¼ wrinkled yellow, ¼ wrinkled green This ratio was actually obtained: there were 31 round yellow, 26 round green, 27 wrinkled yellow, 26 wrinkled green seeds

In order to test his theory for both eggs and sperms, Mendel made the reciprocal backcross, i e., he used a dihybrid for the sperms and a double recessive for the eggs From this mating he obtained 24 round yellow, 25 round green, 22 wrinkled yellow, 26 wrinkled green seeds. The results in both crosses confirmed his theory.

All of these seeds were tested by planting the next year, and their genetic make-up proved to be as demanded by the theory.

Similar backcross experiments were performed with the other five pairs of characters, the results agreed perfectly with those of the foregoing experiments

Thus, step by step, Mendel had built up an overwhelming mass of evidence, consistent within itself, and proving beyond reasonable doubt the truth of the law of independent assortment

TESTING THE CLOSENESS OF FIT OF AN OBSERVED RATIO

Statisticians have developed a number of statistical tests by means of which the investigator can determine how well the results of his experiment fit a particular theory of heredity. One of the most valuable of these is known as the *chi-square test*, so named because of the use of the Greek letter chi (χ) as a symbol (Table 2) It may be applied not only to ratios involving two classes of individuals, such as a 3:1, but to those with three, four, and in fact an indefinitely large number of classes The test answers the question what is the probability of obtaining merely by chance a deviation from the expected ratio greater than that shown by our observed data? For example, in an actual experiment with Drosophila by students the sex ratio obtained was 419 males·466 females The expected ratio in this species is 1 1. Does the observed deviation from a 1.1 ratio here indicate some experimental error or some systematic factor favoring females, or is the result merely such a deviation as one might reasonably expect as a result of chance? The steps in the application of the χ^2 test to this case, with the result, are shown in Table 3 (page 48).

According to the formula for χ^2 it is obvious that the larger the deviation from expectancy the larger will be χ^2 A definite numerical relationship exists between the size of χ^2 as calculated by this formula and the chance of the deviation being exceeded in either direction merely as the

TABLE 2 PROBABILITIES FOR CERTAIN VALUES OF CHI SQUARE (χ^2)*

N = \ P =	0 99	0 98	0 95	0 90	0 80	0 70	0 50	0 30	0 20	0 10	0 05	0 02	0 01	0 001
1	0 0002	0 0006	0 004	0 016	0 064	0 148	0 455	1 074	1 642	2 706	3 841	5 412	6 635	10 83
2	0 0201	0 0404	0 103	0 211	0 446	0 713	1 386	2 408	3 219	4 605	5 991	7 824	9 210	13 82
3	0 115	0 185	0 352	0 584	1 005	1 424	2 366	3 665	4 642	6 251	7 815	9 837	11 341	16 27
4	0 297	0 429	0 711	1 064	1 649	2 195	3 357	4 878	5 989	7 779	9 488	11 668	13 277	18 47
5	0 554	0 752	1 145	1 610	2 343	3 000	4 351	6 064	7 289	9 236	11 070	13 388	15 086	20 52
6	0 872	1 134	1 635	2 204	3 070	3 828	5 348	7 231	8 558	10 645	12 592	15 033	16 812	22 46
7	1 239	1 564	2 167	2 833	3 822	4 671	6 346	8 383	9 803	12 017	14 067	16 622	18 475	24 32
8	1 646	2 032	2 733	3 490	4 594	5 527	7 344	9 524	11 030	13 362	15 507	18 168	20 090	26 13
9	2 088	2 532	3 325	4 168	5 380	6 393	8 343	10 656	12 242	14 684	16 919	19 679	21 666	27 88
10	2 558	3 059	3 940	4 865	6 179	7 267	9 342	11 781	13 442	15 987	18 307	21 161	23 209	29 59

The numbers opposite P (top line) give the probability that χ^2 (in vertical columns) shall exceed the indicated value For example, with $N = 3$ the probability of exceeding by chance a χ^2 of 7 815 is 5 per cent, or one in 20

N is equal to the number of "degrees of freedom" in which the observed ratio may differ from the expected, that is, it is equal to the number of classes the frequencies of which may be filled in arbitrarily With Mendelian ratios, the expected numbers are calculated from the observed total Hence the number of classes that can be filled in arbitrarily is one less than the total number of classes For example, if the expected ratio is 9 3 3 1, there are only three degrees of freedom ($N = 3$), because if three classes are filled in arbitrarily, the fourth is determined by subtracting the sum of these three from the observed total

* From R. A Fisher, "Statistical Methods for Research Workers," Oliver & Boyd, Ltd , Edinburgh and London

result of chance. This relationship is a complex one algebraically, and it is therefore not practicable to calculate the probability for each case. Instead, a table of χ^2 (Table 2) showing χ^2 for a series of probabilities, provided for us by Dr Fisher, is used Referring to Table 2 we note that probabilities (P), shown as decimal fractions, are written along the top

TABLE 3

	Males	Females
Observed numbers	119	466
Expected numbers on 1 1 (e)	142 5	442 5
Deviation from expectancy (d)	23 5	23 5
Deviation squared (d^2)	552 25	552 25
d^2/e	1 25	1 25

χ^2 = Sum of d^2/e = 2 50

line of the table, and under each probability figure is a vertical column of χ^2 values The column headed N must now be consulted and the value of N chosen which represents the number of classes in our ratio. With Mendelian ratios such as 1 1, 3.1, 9 3 3 1, etc., we must choose the N which is one less than our number of classes In our problem therefore, since there are two classes, it will be the number 1. Scanning the χ^2 values opposite $N = 1$ we come to 2 706 This is not far from our calculated χ^2 value of 2 50, and we note that the probability of getting a larger χ^2 than this, or, in other words, the chance of obtaining a greater deviation upon repetition of the experiment, is approximately 0 10, or one in 10

Statisticians have arbitrarily chosen to consider a probability greater than 0 05 (one in 20) as not statistically significant. This means that such a deviation from expectancy is not great enough to indicate the operation of any modifying factor, but is probably merely a deviation due to chance. Since our probability is twice as great, we conclude that the sex ratio actually obtained is well within the range of chance deviation, and hence that we are not justified in regarding the deviation as proof of the operation of some other factor The deviation here, however, may well be the result of systematic causes rather than of chance Our calculations cannot answer this question All our statistical test can do is to tell us how frequently we should expect to get a greater deviation from the theoretical ratio merely as the result of chance.

Let us now apply the χ^2 test to an actual student experiment involving two pairs of genes, in which the expected ratio was 9:3:3.1 The animal used was Drosophila. A recessive mutant known as brown eye was

crossed with a recessive known as scarlet eye The genes show independent assortment. The F_1 hybrids are normal red-eyed F_1 matings were made and the F_2's observed The expected F_2 ratio is 9 red 3 brown 3 scarlet 1 white In this case the double recessive results in absence of pigment. The results and the calculated χ^2 are shown in Table 4

TABLE 4

	Red	Brown	Scarlet	White
Observed numbers	1,134	430	465	133
Expected on 9 3 3 1 (*e*)	1 217	405	405	135
Deviation from expectancy (*d*)	83	25	60	2
Deviation squared (d^2)	6,889	625	3,600	4
d^2/e	5 7	1 5	8 9	0 03

χ^2 = Sum of d^2/e = 16 13

Scanning the values of χ^2 opposite $N = 3$, in accordance with the rule mentioned above, we find a χ^2 of 16 27 under the probability of 0 001 This tells us that the deviation from the expected ratio could have been exceeded by chance only once in 1,000 trials Evidently some explanation other than chance is to be sought Whether or not the deviation from expectancy in this experiment is due to experimental error, differential viability, differential rate of development of the flies, or some other factor or combination of factors must be sought by further study and experiment

PROBLEMS

1. In guinea pigs, the gene *C* for black color is dominant over the gene *c* for albino The gene *R* for rough fur is dominant over the gene *r* for smooth fur In the table below, the results are given for five separate matings Give the most probable genetic formulas for the parents in each mating (The formulas may be obtained by inspection)

	Black Rough	Black Smooth	Albino Rough	Albino Smooth
(*a*) Black smooth × albino smooth	0	18	0	14
(*b*) Black smooth × albino rough	25	0	0	0
(*c*) Black smooth × albino rough	10	8	6	9
(*d*) Black rough × albino rough	15	7	16	3
(*e*) Albino rough × albino rough	0	0	32	12

2 If a pure variety of peas showing the character tall (*TT*) and terminal flowers (*aa*) is crossed with a dwarf variety (*tt*) having axial flowers (*AA*), and the hybrids are allowed to self-fertilize, what will be the visible ratio among their offspring?

3. What is the chance that any tall axial plant produced by the hybrids in the preceding problem is homozygous for both genes? What is the chance that any tall terminal plant is homozygous for both genes?

4. Show the result of crossing a dihybrid from Problem 2 with a double-recessive (short terminal) plant

5. If a pure variety of peas showing the dominant characters tall (*TT*), axial flowers (*AA*), violet flowers (*BB*) is crossed with a variety showing the recessive characters dwarf (*tt*), terminal (*aa*), white flowers (*bb*), and the trihybrids are allowed to self-fertilize, what is the expected visible ratio among the offspring of the trihybrids?

6. Show the results of a backcross of one of the trihybrids in the preceding problem to a dwarf, terminal, white-flowered plant

7. In packages of seeds of supposedly pure varieties of peas purchased at seed stores, it is common to find both yellow and green peas in the same package, whereas the seeds in a given package are usually all round or all wrinkled Mendel observed this difference in color in seeds of pure varieties (see his paper, referred to in footnote, p 6) How does he explain it?

8. Write out the formulas for the gametes produced by an organism hybrid with respect to four genes, as *AaBbCcDd* What chance have the offspring of two such hybrids to be *aabbccdd*? Assuming that dominance is complete in all four genes, what proportion of the offspring of two such hybrids will show all four dominant effects?

9. Starting with two pure-breeding varieties of peas—round green (*RRyy*) and wrinkled yellow (*rrYY*)—show how you might develop, with the least labor and in the fewest possible generations, a pure-breeding round yellow variety Show all crosses and test matings

10. In cats, solid-black fur (*aa*) is recessive to wild tiger pattern (*AA*) With the genes affecting tail length, dominance is lacking *TT* stands for the tailless (Manx) cat, *tt* stands for the normal long-tailed cat the hybrid, *Tt*, is bobtailed What will be the visible ratios among the offspring of the following matings (use the fractional method on these)

a *aaTt* × *Aatt*

b *aatt* × *AaTt*

c *AaTt* × *AaTt*.

11. In Mendel's monohybrid experiments with his seven pairs of characters, two, those involving flower color and pod color, showed the largest deviations from the expected 3 1 ratio in the F_2 With flower color he obtained 705 violet-reds to 224 white Calculate χ^2 and determine from the χ^2 table whether this is a statistically significant deviation

12. With pod-color differences Mendel obtained in F_2 428 greens to 152 yellows Calculate χ^2 and determine the significance of the deviation from a perfect 3.1 ratio

13. By means of the χ^2 test, calculate the probability of obtaining a greater deviation from the expected 9 3 3 1 ratio than Mendel did in his experiment with round yellow dihybrids (as given on page 38 herein)

14. In one of Mendel's test experiments his theory demanded a ratio of 2.1. The ratio he obtained was 60.40 In order to check the deviation from the expected ratio he repeated the experiment, obtaining on the second trial 65:35 Calculate the χ^2 of the first trial and state whether you would have considered it necessary to repeat the experiment

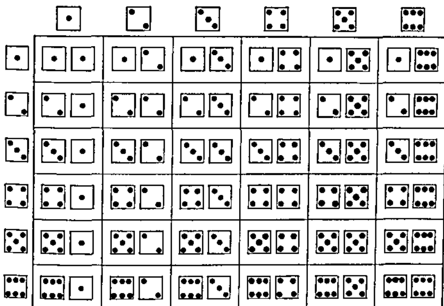
15. Calculate the expected ratio from a cross between a roan horned bull and a red homozygous polled cow

16. Calculate the expected ratio from a mating of a white heterozygous polled bull and a roan heterozygous polled cow.

17. In the Hereford breed of beef cattle the general color is red, with white face and white on neck and underparts Another breed of beef cattle, Aberdeen Angus, is solid black. Black hair color is dominant over red The white face, inherited independently of general body color, is dominant Calculate the expected result of a cross between a homozygous black polled Aberdeen Angus with a homozygous horned Hereford

18 Calculate the expected ratio from a backcross of one of the hybrids from Problem 17 with a horned Hereford

19. Calculate the expected ratio from a mating of two of the hybrids obtained in Problem 17



20. Independent assortment is illustrated in throwing a pair of dice Using the above drawing for reference, show by means of bar graphs the chances of obtaining all possible numbers of *spots* in throwing a pair of dice Draw vertical bars to show frequencies, with the bar for the smallest number of spots at the left and progressively larger numbers of spots to the right How do you account for the fact that 7 is the most probable number of spots? What other numerical regularities can you discover in the diagram?

21. Given a pure-breeding variety of black rough guinea pig (*CCRR*) and a pure-breeding variety of albino smooth (*ccrr*), show how you would produce in the fewest possible matings a pure-breeding variety of black smooth (*CCrr*) guinea pig (Black and rough are both dominant) Number the matings you would make in chronological order and indicate the number of offspring you would obtain in your final test mating in order to be reasonably sure that you had accomplished your aim

4

THE REDISCOVERY OF MENDEL'S WORK

Mendel's biographer, Iltis, believes that the chief reason why Mendel's work was so little noticed or understood, either by the members of the Brunn Society for the Study of Natural Science, before whom it was described orally, or by scientists in general, was the atmosphere of intense interest in Darwin's theory of the origin of species, which had been published just six years previously Iltis writes:[1]

> The psychological law that the contents of consciousness are sharply restricted applies, not only to individuals, but to generations, and since the consciousness of the epoch was entirely filled by the flood of ideas contained in the Darwinian theory and its consequences, people would not trouble themselves to make a place in their minds for the profound and peculiar ideas of Mendel, even though these were concerned with a kindred field
>
> The basic notion of Darwin's doctrine was the variability of species, whereas the basic idea of Mendel's (though none of Mendel's hearers nor even the lecturer himself had clearly recognized this) was the constancy, if not of species, at least of their elements, of characters, and of the heredity factors producing these The trouble was this, and this only, that the time was not yet ripe for the understanding of Mendel's laws either in Brünn or elsewhere.

"BOTANICAL MATHEMATICS"

Furthermore, according to Iltis, "many of Mendel's auditors must have been repelled by the strange linking of botany with mathematics" In Mendel's day, the quantitative study of biology in its various branches had only begun Mathematics as a necessary tool for the biologist had not yet been generally recognized To certain minds it is possible that Mendel's laws may have seemed too mathematical to be true for living things

A part of the difficulty in winning acceptance of the new ideas undoubtedly related to the fact that the laws involve the idea of probability, or statistics Among the various branches of mathematics, statistics is a late arrival Few biologists were trained in those days to think in

[1] Hugo Iltis, "Life of Mendel," by permission of W. W Norton & Company, Inc, New York

terms of probability. There is still great need in this country of improvement in the teaching of probability in high-school and college mathematics The topic usually appears near the end of the algebra textbook, where it is likely to be omitted in the rush at the end of the course Many years experience in teaching Mendel's laws to the uninitiated convinces the writer that to some intelligent minds there is, at first contact, something difficult and baffling in the ideas involved This difficulty seems in most cases to be due to unfamiliarity with the idea of probability

From the point of view of the reader who already understands the laws, Mendel's paper is a model of scientific exposition Its logic, orderliness, and accuracy could hardly be improved However, the algebraic method of presentation may have deterred some readers The graphic representation in checkerboard diagrams, as illustrated in earlier chapters, is probably easier for the beginner

REASONS FOR LACK OF APPRECIATION OF MENDEL'S WORK

Mendel's position as a priest and teacher in a small secondary school was probably not in his favor in certain quarters Had he been a member of a great university, he would no doubt have obtained a more sympathetic hearing Although copies of the publication in which his paper appeared were circulated to more than 120 institutions, including 10 or more in the United States,[1] it is natural that an obscure journal should not have received the same careful reading as did the better-known scientific periodicals.

Obviously, another reason why the time was not yet ripe for the recognition of Mendel's discovery was the lack of knowledge of what went on inside the cell. It is recalled that knowledge of the behavior of the chromosomes during mitosis, meiosis, and fertilization was still a closed book.

NAGELI AND MENDEL

Karl W. Nageli (1817–1891), professor of botany at Munich, Bavaria, was one man at least who from his own interests and researches should have appreciated Mendel's work Nageli had for years been studying hybridization in plants and writing on heredity and evolution Mendel had great respect for Nageli, and in 1866 wrote him a letter enclosing a copy of the paper on peas From Nageli's answer and from notes he made on Mendel's work it is clear that he regarded the formation of pure eggs and sperms by a hybrid (as reported by Mendel) an impossibility. He thought that the constant forms which had segregated out of Mendel's hybrids re-

[1] M J Dorsey, Appearance of Mendel's Paper in American Libraries, *Science*, Mar 10, 1944

quired to be tested further and predicted that they would sooner or later vary once more. It is well to recall that this doubt had apparently occurred to Mendel also, for he had tested out hybrids on this very point—in some cases through as many as six generations Nevertheless, Nageli was not satisfied and asked that Mendel send him some of his seeds for testing at Munich Mendel replied, sending 140 labeled packages of seeds with directions for testing them Nageli planted a number of the test seeds, but he never made the promised series of control experiments, and, according to Iltis, neither in his letters to Mendel nor in his subsequent papers and books do we find any reference to Mendel's work on peas.

Mendel realized the necessity of repeating his experiments with other species. On July 3, 1870, in a letter to Nageli,[1] he stated that he had concluded experiments with *Zea*, *Mirabilis*, and *Matthiola* and that their hybrids behave exactly like those of *Pisum*. These confirmatory experiments were apparently not published in detail They seem to have made no impression on Nageli.

It seems, therefore, that if one of the leading biologists in Europe could thus fail to appreciate the importance of Mendel's work or the necessity of repeating the experiments relating to a field in which that biologist was an authority, it is little wonder that other men less favorably situated should have failed to do so

RESURRECTION OF MENDEL'S PAPER

As late as 1900 there were, according to H F Roberts,[2] only two published works which referred to Mendel's paper on peas. The first of these was a book by a German botanist, Hermann Hoffmann, published in 1869, reporting investigations on the problem of species and varieties in connection with a study of Darwin's theory of evolution The second was a book by W. O. Focke, published in Berlin, 1881, entitled *Die Pflanzenmischlinge* (Plant Hybrids) In one of his references to Mendel, Focke states that Mendel's experiments on peas gave results similar to those obtained by Andrew Knight (an Englishman who about 1825 had reported experiments in hybridizing peas), but that Mendel believed he had found constant numerical ratios among the types produced by hybrids

Apparently a third reference to Mendel's work should be added to this list, for, according to Dorsey, the American botanist L. H. Bailey included a reference to Mendel's work in a paper on crossbreeding and hybridizing in 1892. Bailey, however, had not seen Mendel's paper, but had

[1] Gregor Mendel's Letters to Carl Nageli, 1866–1873, supplement to *Genetics*, **35**:1–29, 1950

[2] H. F. Roberts, "Plant Hybridization before Mendel," Princeton University Press, Princeton, N J , 1929

Versuche über Pflanzen-Hybriden.

Von

Gregor Mendel.

(Vorgelegt in den Sitzungen vom 8 Februar und 8. März 1865.)

Einleitende Bemerkungen.

Künstliche Befruchtungen, welche an Zierpflanzen desshalb vorgenommen wurden, um neue Farben-Varianten zu erzielen, waren die Veranlassung zu den Versuchen, die her besprochen werden sollen. Die auffallende Regelmässigkeit, mit welcher dieselben Hybridformen immer wiederkehrten, so oft die Befruchtung zwischen gleichen Arten geschah, gab die Anregung zu weiteren Experimenten, deren Aufgabe es war, die Entwicklung der Hybriden in ihren Nachkommen zu verfolgen.

Dieser Aufgabe haben sorgfältige Beobachter, wie Kölreuter, Gärtner, Herbert, Lecocq, Wichura u. a. einen Theil ihres Lebens mit unermüdlicher Ausdauer geopfert Namentlich hat Gärtner in seinem Werke „die Bastarderzeugung im Pflanzenreiche" sehr schätzbare Beobachtungen niedergelegt, und in neuester Zeit wurden von Wichura gründliche Untersuchungen über die Bastarde der Weiden veroffentlicht Wenn es noch nicht gelungen ist, ein allgemein giltiges Gesetz fur die Bildung und Entwicklung der Hybriden aufzustellen, so kann das Niemanden Wunder nehmen, der den Umfang der Aufgabe kennt und die Schwierigkeiten zu würdigen weiss, mit denen Versuche dieser Art zu kämpfen haben. Eine endgiltige Entscheidung kann erst dann erfolgen, bis Detail-Versuche aus den verschiedensten Pflanzen-Familien vorliegen. Wer die Ar-

1*

Figure 17. Facsimile reproduction of page 1 of Mendel's "Experiments Relating to Plant Hybrids." (*From J. Heredity.*) See Appendix B for English translation

taken his reference from Focke De Vries, to be mentioned presently, learned of Mendel's work from Bailey's bibliography. None of these authors, however, seems to have realized that Mendel had discovered an important new law, and their passing references to Mendel apparently attracted no further notice to him Iltis quotes a letter to himself from Focke as follows.

I know that my attention was drawn to Mendel's work by some reference or other in the literature of the 'seventies, but I cannot now remember when or where I first heard of him. I did not read his paper until shortly before the publication of my own book. . . . You ask me as to the impression Mendel's paper made on me when I first read it. I can only say that it seemed to me his statements were well worth checking, and that I regretted not being in a position to repeat his experiments. This would have needed much more time and much more cultivable space than were at my disposal Fluttering the pages of my book I note that on p 492 I have included Mendel among the most trustworthy of observers

In the years following the publication of Focke's book, rapid strides were being made in the branch of biology dealing with the cell and its behavior The nucleus and chromosomes were receiving more and more attention and were coming to be recognized as those parts of the cell especially adapted for the transmission of the hereditary materials Theories of heredity were being proposed and debated On the basis of the newer knowledge of the cell, the old belief in the inheritance of acquired characters was yielding ground

Among the leaders in the debate on the inheritance of acquired characters was August Weismann, who is most famous for his germ-plasm theory of heredity and development He regarded the chromosomes as the material basis of heredity and looked upon these as passing unchanged from generation to generation, showing on theoretical grounds that there must be a reduction division at the formation of the reproductive cells The hereditary materials were, in his view, not made up from an assemblage of particles released by the body cells into the blood and later aggregated in the reproductive cells, as Darwin had suggested, but were in each generation received as such from the parents and were only temporarily protected and nourished by the body until the time came for them to be passed on to the next generation. The body cells, as well as the sperms and eggs, arose by cell division (mitosis) from the fertilized egg After serving their function the body cells eventually died, while the reproductive cells, potentially immortal, were passed on to the next generation

With biologists stimulated to take up again the study of heredity, it is perhaps not surprising that in the last decade of the nineteenth century a number of investigators should have begun an attack on the problem

by crossing plants Nevertheless, there is dramatic interest in the fact that three botanists, in three different countries, independently began such experiments and, unknown to one another, obtained within a short period of time results confirming Mendel's discovery, while not one had read Mendel's paper before beginning his own experiments.

The first botanist to report his results was Hugo De Vries of Holland. In March, 1900, he published two papers, one in French and one in German, *giving results of experiments begun in 1892 The former paper*, appearing in the *Comptes rendus* of the French Academy of Science, was very brief, containing merely an abstract of his conclusions It mentioned several species of plants used in the experiments The pea was not one of them Segregation was reported, and the ratios agreed perfectly with those of Mendel The terms "dominant" and "recessive" were used in the same sense as used by Mendel, but Mendel's name was not mentioned.

The German paper, seven pages in length, was also little more than a summary It was published in *Berichte der Deutschen Botanischen Gesellschaft* (Reports of the German Botanical Society) In it, De Vries lists species of plants belonging to more than a dozen genera with which he had experimented beginning in 1892 and which were found to follow Mendel's laws of dominance and segregation In this paper he gives Mendel credit for being the original discoverer of these laws, in the following words:

> These two propositions were in their essential points drawn up long ago by Mendel for a special case (peas) They were, however, not appreciated and sank into oblivion They possess, according to my own experiments, general validity for true hybrids This important paper is so seldom referred to that I myself first learned of it after I had finished the majority of my experiments, and had deduced the propositions mentioned

De Vries also gives results confirming the law of independent assortment, but does not mention Mendel as having also discovered this law In a footnote he cites the book by Focke already referred to

The implication in the use of the phrase "special case" seems hardly justified, for Mendel had also performed experiments with two species of beans (reported in the paper on peas), which were in perfect agreement with those in peas In two other species of beans his results were only in partial agreement, but were correctly explained by him as falling under the same laws, with the addition of a supplementary principle (the factor principle), discussed in a later chapter

Mendel was modest in making any claims for his laws beyond the point directly supported by the facts In one place in his paper he states:

> Whether the variable hybrids of other plant species observe an entire agreement must also be first decided experimentally. In the meantime we may assume

that in material points an essential difference can scarcely occur, since the unity in the developmental plan of organic life is beyond question.

The second botanist to confirm Mendel's results was Carl Correns of Tubingen, Germany, who interestingly enough was one of Nägeli's former students His paper was published in the same German periodical as De Vries', in April, 1900, in the very next issue. It is ten pages in length and entitled "G Mendel's Law Concerning the Behavior of the Descendants of Racial Hybrids" Correns states that the publication of De Vries' paper (the one in French) induced him to write his own; that in his experiments with varieties of corn and peas he had come to the same conclusions as De Vries and that he also believed, as De Vries obviously did, that he had discovered something new; but that later he had found that Gregor Mendel in the sixties had obtained not only the same results but had given exactly the same explanation, so far as this was possible in 1866 "To bring it up to date," says Correns, "one needs merely to substitute 'egg cell' or 'egg nucleus' for germ cell or germinal vesicle, and 'generative nucleus' for 'pollen cell'" Correns mentions the fact that Mendel had confirmed in beans the results of his experiments with peas and that Mendel supposed that the law held in many other cases. His opinion of Mendel's work is expressed as follows:

> This paper of Mendel's to which Focke refers in his "Pflanzenmischlinge," but without giving it its due, and which had received scarcely any notice, is among the best works ever written upon the subject of hybrids, in spite of numerous criticisms which can be made of it in incidental matters such as terminology.

Correns disagrees with De Vries' claim that dominance is a universal rule and cites cases in which the hybrid is intermediate. In this he followed Mendel who, as we have seen, found a similar case. Correns, however, made the mistake of regarding Mendel's laws as applicable almost exclusively to racial hybrids Mendel had suggested that there was no essential difference in the mechanism of heredity between racial hybrids and species hybrids, and this has been found to be true.

The third man to confirm Mendel's laws of dominance and segregation was Erich Tschermak, a botanist of Vienna His paper, consisting of seven pages, was published in June of the same year in the same periodical as the papers of De Vries and Correns. His experiments were confined to peas Although he does not give his actual numbers, his ratios produced by monohybrids were as 3·1. No mention is made of experiments on independent assortment Tschermak states that he was stimulated to begin his crossing experiments on peas in 1898 by Darwin's experiments on the effects of self-fertilization and cross-fertilization, and that he was especially interested in the group of plants to which peas be-

long since they furnish an exception to the general rule that crossing different individuals and varieties has a beneficial effect on the offspring. His observations of dominance and segregation seem to have been incidental

In a postscript to his paper Tschermak states "The simultaneous discovery of Mendel by Correns, De Vries, and myself, seems to me especially gratifying. I, too, as late as the second year of my experiments, believed I had discovered something entirely new"

ILTIS' TRIBUTE TO MENDEL

I should like to conclude this chapter by quoting from the beautiful tribute to Mendel penned by his fellow countryman and biographer Hugo Iltis

This almost simultaneous rediscovery of the writings of Gregor Mendel by three investigators working quite independently one of another was remarkable enough to rivet the attention of biologists the world over Mendel's time had at length come, and this to an extent far beyond anything of which he had dreamed A mighty edifice has been erected upon what seemed, though wrongly, to be a very slender foundation. The little essay published in the "Proceedings of the Brunn Society for the Study of Natural Science" has given a stimulus to all branches of biology, with the result that the study of heredity, in its neomendelian form of genetics, has become one of the most important branches of contemporary research. . . . The progress of research since the beginning of the century has built for Mendel a monument more durable and more imposing than any monument of marble or bronze, inasmuch as, not only has "mendelism" become the name of a whole vast province of investigation, but all living creatures which follow "mendelian" laws in the hereditary transmission of their characters are said to "mendelise" In these words Mendel's name will be immortalised as long as science endures.

All the same it was felt by many that a memorial to Mendel ought to be erected in the place where he had lived and worked and died This was when the work had already become famous throughout the world, but in Brunn most of the elders had forgotten him, and few of the young folks had ever heard of him Brunn, in fact, was hard to move A great many lectures had to be delivered, and much propaganda was needed in the newspaper press, before some understanding of the importance of "mendelism" could be knocked into the hard heads of the Brunners Indeed, for those who know little and care less about biology, its importance is not obvious, and the doctrine is somewhat hard to understand . . .

Of course it was far from easy to arouse in the minds of those whose only claim to intelligence was the possession of such "common sense" an understanding of Mendel's importance in the world of modern thought Not a few of the influential residents of Altbrunn protested against the erection of the memorial in the Klosterplatz on the ground that this would involve the banishment of the booths and roundabouts which at fair-time amused people and brought money

into the town Others, pluming themselves on being advanced thinkers, objected to the raising of a monument to a priest

Still, within a few years it was found possible to reconcile Brünn to the idea of the Mendel memorial In fact most of the money was collected locally, although part of the sum came from abroad through the instrumentality of a large



Figure 18. Memorial to Gregor Mendel in Brunn. Statue by Theodor Charlemont. (*From Iltis, "Life of Mendel," W. W. Norton & Company, Inc*)

international committee to which more than 150 investigators of all parts of the world belonged. Competitive designs were asked for, and that of Theodor Charlemont of Vienna was accepted. In the Charlemont statue we see the figure of Mendel as a young priest dressed in the conventual robes standing in front of a hedgerow of peas and beans (the classical objects of his investigations), and, with outstretched hands, fingering flowers and leaves The face, finely intellectual, is looking out thoughtfully into the distant future Charlemont had nothing better than photographs to work from, but the result is as lively and natural as could be

wished. On the face of the pediment, immediately beneath the standing figure, is the inscription

TO THE INVESTIGATOR
P GREGOR MENDEL

1822–1884

Along the lowest part of the front is a further inscription

ERECTED IN 1910 BY THE FRIENDS OF SCIENCE

Between these two inscriptions and upholding the upper one, in slight relief, are the figures of a youth and a maiden, nude and kneeling, with joined hands This is a subtly allegorical allusion to the far-reaching importance Mendel's genetic laws are likely to have upon human life. The monument is not only a noble tribute to Mendel but an extraordinarily beautiful example of the sculptor's art

The unveiling of the memorial took place on October 2, 1910 All honor was then paid to the life and work of the retiring investigator who in the little garden near at hand had been so happy among his flowers and his bees To him were now applicable the somewhat crude but thoughtful verses he had himself in boyhood penned in memory of Gutenberg

May the might of destiny grant me
The supreme ecstasy of earthly joy,
The highest goal of earthly ecstasy,
That of seeing, when I rise from the tomb,
My art thriving peacefully
Among those who are to come after me

That was in the year 1910, and William Bateson, as spokesman of the British mendelians, delivered a speech extolling the power of science to bring the nations together, concluding with Schiller's words "Alle Menschen werden Brüder"

During the years that followed, men forgot their brotherhood In the mad days of barbarism and savagery while the war was raging and after it, those who should have been the devotees of science were devoting themselves to the cultivation of hatred and to the arts of destruction. Slowly, however, the world returned to its senses In 1922 a century had passed since Gregor Mendel first saw the light in the little Silesian village where he was born The scientific press throughout the world made much of this centenary, and a commemorative volume was issued In Brünn a centenary festival was held, and for the first time in eight years men of science from all nations met together there in amity The debates that had been raging were stilled sub specie aeternitatis In front of the Mendel monument, speeches were delivered in German, Czech, English, and French The Czechs and the Germans, the divided races who dwell in Mendel's homeland, their mutual enmity forgotten if only for a moment, joined hands beneath the statue of the dead investigator In this matter, likewise, Gregor Mendel had worked a miracle.

That was nearly ten years ago now, and with every year his influence is more widespread He is modifying our whole outlook on life, he has helped us amaz-

ingly to increase "the fruits of the earth in due season"; and he has opened up paths of research which seem likely to enable mankind to remould its very self. Thus his name will always live as a pioneer of research, as a pathfinder on the way to the new time; and the coming generations will never forget Gregor Mendel as one of the chief among those who have brought light into the world

PROBLEMS

1. List the probable reasons for the failure of biologists to appreciate Mendel's paper on plant hybridization at the time of its publication, and for their failure to repeat his experiments during the next 30 years or more

2. What part did Nageli play in the neglect of Mendel's work?

3. What further steps might Mendel have taken to gain a hearing for his theory of heredity?

4. With what other plants did Mendel confirm his experiments with peas?

Note The answers to the following questions may be found from a reading of Mendel's paper

5. What reasons does Mendel give for the failure of earlier experimenters to discover the laws of heredity?

6. What were his reasons for selecting peas as his experimental material?

7. What precautions did Mendel take to ensure the homozygosity of his original stock?

8. What control did he exercise on the possibility of cross-pollination by insects?

9. What evidence did he obtain that the egg and pollen are equivalent in the capacity to transmit hereditary factors?

10 Why did Mendel consider the solution of the problem he chose to work on so important?

5

CHROMOSOMES AND MENDEL'S LAWS

At the time of Mendel's experiments on peas the existence of chromosomes as constant cellular bodies had not been discovered Mendel therefore made no reference to chromosomes. It remained for an American biologist, W. S. Sutton (1902, 1903), to explain in full the operation of Mendel's laws in the light of chromosome behavior His explanation was based largely upon discoveries in chromosome behavior made by the German biologist Boveri.

During the 1870s and 1880s chromosomes received gradually more and more attention from biologists. The cells of many species of plants and animals were examined, and in all cases, except in some of the simplest one-celled forms, chromosomes were found Each species was observed to have a definite number of these bodies, appearing always in pairs (an exception in the case of sex chromosomes is noted in Chap. 9), the members of each pair having come from the parental sperm and egg respectively. In a given species the pairs were frequently distinguishable from one another in size and shape

Rapid progress in the understanding of chromosomes was made possible by improvement in the methods of studying cells, especially the technique of staining for the purpose of bringing into visibility the various components of the cell. One of the characteristics common to all chromosomes is the special ability to take up basic dyes, a characteristic which makes easy their sharp differentiation from other cellular structures.

MITOSIS

In the period mentioned above, observations on the behavior of the chromosomes at cell division pointed unmistakably to their having some function in heredity, thus it was soon established that the usual method of cell division was not a simple division of the cell nucleus into two parts, followed by a similar division of the cytoplasm, as had been supposed, but that the chromosomes passed through a definite series of changes and movements adapted to ensure the transmission to each of the two daughter cells of a set of chromosomes identical with that of the

mother cell. This process, known as *mitosis* (*mitos*, thread) was named by Flemming, one of the discoverers of mitosis, in 1882, in reference to the fact that at one stage the chromosomes appear as slender threads As we know today, the primary function of mitosis is the equal distribution of the genes, which are on the chromosomes, to the two daughter cells

The most favorable material for the observation of mitosis is tissue in which rapid cell division is taking place, such as the growing root tips of

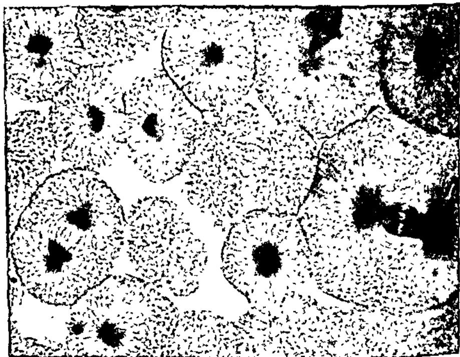


Figure 19. Photomicrograph of a section of the early embryo of the whitefish (*Coregonus clupeiformis*), showing cells in various stages of mitosis (*General Biological Supply House, Chicago*)

plants and the early embryonic stages of animals (Figs. 19 and 20) The process can be observed, however, in any growing tissue, even in that of mature animals, for instance, in the skin of mammals

In studying mitosis the tissues are usually placed in chemicals which rapidly kill them and fix the cells and cell components in their normal relations, thin slices are then cut and stained. In numerous instances, however, mitosis has been observed and photographed in living cells. For the photographing of living chromosomes, ultraviolet rays are most effective (Fig 22).

Mitosis always exhibits a typical succession of stages, but the process is a continuous one, each stage merging into the next The entire process



Figure 20. Mitosis in the early embryo of the whitefish In this species, during the early stages of embryonic development, the interphase is usually not observed, the telophase passes at once to the early prophase (*Photomicrographs, General Biological Supply House, Chicago.*)

may require from one to several hours Let us now examine briefly the successive stages, making use of the photomicrographs of the whitefish embryo (Figs 19 and 20) and of the diagram (Fig. 21) in order to visualize the process

1. The Interphase. This is the stage characteristic of cells in nongrowing tissue The term resting stage is also applied to it since no visible nuclear changes are taking place, although, of course, the cell may be

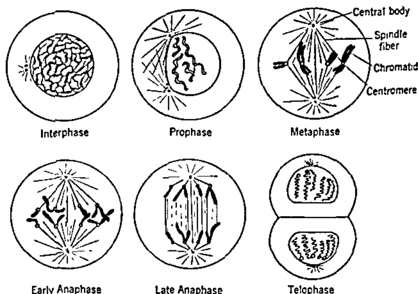


Figure 21. Diagram of the successive stages of mitosis in a species having two pairs of chromosomes.

very active in the metabolic sense. Note in Fig 21 that the nucleus appears as a rounded body, filled with chromatin granules apparently held in place by a fine network of fibers In reality it contains a mass of tenuous coiled threads, representing the chromosomes Surrounding the nucleus lies a delicate membrane The chromosomes, as such, ordinarily cannot be identified, owing to their finely dispersed condition.

2. The Prophase. As an indication that the cell is preparing to divide, the chromatin of the resting cell gradually condenses into visible threads At first each thread is seen to be made up of two identical strands, or *chromatids* The chromosomes gradually condense and shorten as a result of the spiraling of the threads Each chromosome bears a constriction at a definite point, the locus of a tiny body known as a *centromere*,[1] which is regarded as the dynamic center of the chromosome.

[1] In works on cytology in the United States the term *kinetochore* is sometimes used as a synonym for *centromere* In order to show the length to which biological nomen-

In the meantime, on one side of the nucleus a spindle-shaped mass of viscid cytoplasm is forming, appearing in stained cells to be made up of fibers. The nuclear membrane soon breaks down, and the *spindle* comes to occupy the center of the cell, the thickest part of it lying on the equator, or future division plane of the cell The chromosomes move to take up their position on the spindle at the equator

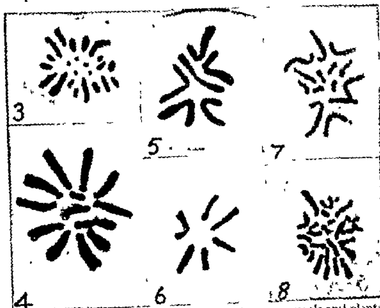


Figure 22. Polar views of metaphase of mitosis in animals and plants (3) A grasshopper, *Locusta migratoria*, ♂, $2n = 22 + X$ (*Koller, unpublished*) (4) A plant, *Eremurus spectabilis*, root tip, $2n = 14$ ×2,000 (*Upcott*, 1936) (5) A plant, *Tradescantia bracteata*, pollen grain, $n = 6$ (6) A plant, *Brodiea uniflora*, pollen grain, $n = 6$. (*La Cour*) (7) A plant, *Puschkinia libanotica*, root tip, $2n = 10 + 4$ ff. ×1,500. (*Darlington*, 1936) (8) A plant, *Tricyrtis hisla*, root tip, $2n = 26$ (*La Cour*) (*From Darlington, "Recent Advances in Cytology," 2d ed, Blakiston Division, McGraw-Hill Book Company, Inc*)

3. The Metaphase. In this stage the chromosomes lie in the equatorial region of the cell The centromeres are lined up on the equator of the spindle, while the remaining portions, or bodies, of the chromosomes may lie off the equator

In the equatorial view of the metaphase (Fig 20) the chromosomes appear as a single row of objects In the polar view (Fig 22) they appear

clature may go, Professor Franz Schrader in his book "Mitosis The Movements of Chromosomes in Cell Division," Columbia University Press, New York, 1944, lists 27 terms that have been applied as names for the centromere since its discovery in 1894.

spread out in platelike formation The polar view is the preferred one for the counting of chromosomes.

In animal cells, unlike most plant cells, small bodies known as *central bodies* are seen at the poles of the spindle, and from these fibers radiate in all directions, forming the so-called *asters* (*aster*, star). The central bodies are self-duplicating structures in successive cell divisions

4. The Anaphase. Each centromere divides equally, thus completing the division of the chromosome into two daughter chromosomes. As the identical sets of daughter chromosomes move apart toward the opposite poles of the spindle the centromeres take the lead Each chromosome is apparently pulled by its attached spindle fiber. The chromosome bends at the point of spindle-fiber attachment, owing to the resistance of the cytoplasm to the passage of the chromosome. The forces which cause this movement are probably complex, they have not been satisfactorily explained in chemicophysical terms

5. The Telophase. Upon reaching the poles of the spindle, each group of chromosomes enters into the formation of an interphase nucleus, the chromosomes losing, in most species, their visible identity, but retaining, it is supposed, their fundamental organization In some early embryos the formation of typical interphases does not occur, but the telophase passes directly into early prophase of the next division.

The division of the cytoplasm into two parts is accomplished in animal cells by constriction at the equator; in plant cells with rigid cell walls it is brought about by the formation of a new cell wall in the equatorial plane

As a consequence of the process of mitosis, repeated again and again during development, every cell in the body should come to have a full complement of chromosomes identical with that of every other cell. In general this expectation is realized, although there are numerous exceptions. The most common exception is the duplication of the entire complement of chromosomes without a cell division, resulting in what is known as polyploidy, discussed in a later chapter. There is good evidence that each chromosome is functionally a chain of genes arranged in a definite linear order and that prior to the visible splitting of the chromosomes each gene in the chain is duplicated The details of this process of duplication are as yet undiscovered

The regularity, orderliness, and apparent efficiency of the process of mitosis make it one of the most interesting activities displayed by cells. Its importance in the development of the organism can hardly be overestimated, for it is the process that ensures that the individual shall develop as an orderly and symmetrical unit If, as sometimes happens, there is an abnormal mitosis, such as the failure of one chromosome to go into the nucleus that would normally receive it, an abnormality may result in

the particular part of the developing individual derived from that cell An abnormal number of chromosomes, other than polyploidy, commonly leads to lessened viability of the organism Normal development and normal function depend upon normal chromosome balance

MEIOSIS

At one stage—and one stage only—in the life cycle of sexually reproducing organisms, a peculiar modification of the process of mitosis described above takes place This modification is known as *meiosis* (*meiosis*, reduction) In animals it occurs in those cells which are undergoing maturation into sperms and eggs, in plants it takes place during the formation of the spores Essentially, the process consists of two successive cell divisions accompanied by only one duplication of the chromosomes, resulting in a reduction in the number of chromosomes from the double set found in the body cells to a single set

An obvious function of meiosis is the maintenance of a constant chromosome number in the species, for without it, as a consequence of fertilization, there would be a doubling of the chromosome sets in each generation This of course would produce an impossible situation if continued for many generations, since the cells would soon be unable to contain the chromosomes A second function of meiosis is to serve as the physical mechanism for the segregation, assortment, and recombination of the genes It is of prime importance in the production of variability in living things

The typical steps in the process of meiosis will be described by considering in chronological order the events in the formation of the sperms and eggs in animals (Fig 23) Further details on some phases of the process will be considered in Chap 8 on Linkage and Crossing Over

Spermatogenesis. During the period of sexual maturity in animals, the sperm (spermatozoa) are formed in the testes from reproductive cells known as *spermatogonia* These cells, along with all other cells in the body, have come from the fertilized egg through a series of mitotic divisions They therefore contain the double set of chromosomes characteristic of the species The final spermatogonial divisions result in cells known as *primary spermatocytes*, which in preparation for meiosis enter upon a period of growth

In the early prophase of the spermatocyte, the chromosomes make their appearance as fine single threads, in contrast to their appearance as double threads in ordinary mitosis The threads soon come together side by side in pairs (*synapsis*). One chromosome of each pair is maternal in origin, the other paternal While in synapsis or before, the threads frequently show granules (*chromomeres*) of varying sizes and shapes along

their length, giving them the appearance of strings of beads The pattern of the granules on the members of a synaptic pair is identical Pairing takes place between identical chromomeres.

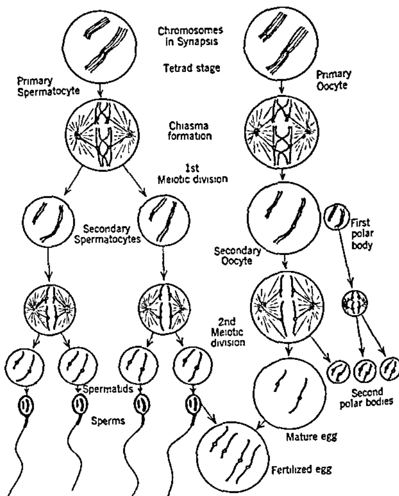


Figure 23. Diagram of spermatogenesis, oögenesis, and fertilization in animals, designed especially to show the process of meiosis.

The paired chromosomes shorten and thicken, each chromosome bearing one *centromere*, as described under mitosis. After a time each pair is seen to be made up of four half-chromosomes, or *chromatids*, the result of the formation of two chromatids from each chromosome The two original centromeres, however, remain undivided. Groups of four chromatids are known as *tetrads*. While in the tetrad stage the chromatids usually form one or more characteristic figures known as *chiasmata* (sin-

gular, *chiasma*, from the Greek, meaning two crossed lines) The tetrad stage is of special interest because it is at this time that the genes on the paternal and maternal chromatids are in position to exchange places with one another. This exchange, which is known to be a regular occurrence, results in a recombination of paternal and maternal genes It is discussed in a later chapter under the head of crossing over

The tetrads line up on the metaphase plate The undivided centromeres, each with two chromatids, move apart and proceed to the opposite poles of the spindle. The two resulting cells, known as *secondary spermatocytes*, undergo in some species a short resting stage; in others they enter at once upon the second division In either case, this second division is like an ordinary mitosis in that each centromere divides into two; then each one of the two moves to an opposite pole, taking with it the rest of the chromosome

The cells resulting from the second division are known as *spermatids* As a consequence of the two cell divisions of meiosis, accompanied by only a single chromosome doubling, each spermatid obviously possesses just half the number of chromosomes characteristic of the species Furthermore, this single set of chromosomes consists of a sample of every chromosome pair, and hence of every gene pair, characteristic of the species (an exception will be noted in the discussion of the sex chromosomes in a later chapter).

Reduction now being complete, the spermatids have only to undergo a process of cytoplasmic differentiation to become the highly specialized cells known as sperms. This differentiation consists in the condensation of the nucleus into a streamlined head, and the development of a whiplike locomotor organ (tail) adapted for propelling the sperm head, with its contained chromosomes, to the egg

Oögenesis. From the standpoint of chromosome behavior, the maturing of the egg follows a pattern similar to that of the sperms The differences that exist have to do with the special role of the sperm and the egg in fertilization and development In the ovary, the immature egg, or *primary oocyte*, grows to a relatively huge size in preparation for the cell divisions of early embryonic development Even in mammals the egg may attain a mass one thousand or more times that of an ordinary cell The difference in size of the egg and the sperm is still greater (Fig 24) The characteristic growth of the oöcyte is due largely to an accumulation of stored food.

In mammals the first meiotic division commonly takes place before the oöcyte is released from the ovary The spindle forms near the surface and at right angles to it, so that when the oöcyte divides, one of the cells (*polar body*) receives very little of the cytoplasm, most of it being retained by the other cell, the *secondary oöcyte* The second division usually



Figure 24. Photographs of mouse eggs. ×600. *Top*· Egg removed from ovary *Bottom* Fertilized egg from oviduct 20 hours after copulation Two polar bodies and sperm in perivitelline space. (*From Lewis and Wright, Carnegie Inst. Wash Pub* 459, 1935)



Figure 25 Photographs of certain stages in meiosis in living cells of two species of grasshoppers (1–3) Late prophase in *Stenobothrus lineatus* (*Belar*, 1927) (1) Living cells (2) The same cells after fixation with osmium tetroxide vapor and Flemming solution (3) The same cells after staining (4–7) Living chromosomes of *Melanoplus femur rubrum*, taken by ultraviolet light (*After Lucas and Stark*, 1931) (4) Late telophase before meiosis ×1,800 (5) Early prophase ×1,800 (6) First anaphase ×1,200 (7) First telophase ×1,200 (*From Sansome and Philp "Recent Advances in Plant Genetics," 2d ed, Blakiston Division, McGraw-Hill Book Company, Inc*)

takes place only after the entrance of a sperm at fertilization Again as in the first division, the partition of the chromatin is equal but that of the cytoplasm is very unequal, resulting in the formation of a second polar body. In some species the first polar body may divide The three polar bodies should be thought of as vestigial eggs, being deficient in

cytoplasm, they eventually disintegrate. The functional egg and the polar bodies together are homologous with the four sperms.

In Fig 25 are reproduced photographs, taken under high powers of the microscope, of certain stages in meiosis of two species of grasshoppers 1 to 3 show that the form of the chromosomes is not altered by the treatment given them in fixation and staining, excepting a slight shrinkage

Fertilization. Fertilization consists of the penetration of the egg by the sperm, and the fusion of the egg and sperm nuclei into one. Obviously, the fusion nucleus contains a double set of chromosomes, since each gamete brings into the union a single set Throughout development and growth the double set is carried along by mitosis to all the cells of the body

The German biologist O Hertwig, in 1875, observed for the first time all the steps in fertilization, including the union of the chromosomes of the egg and the sperm in a single nucleus. The species he observed was an invertebrate animal known as a sea urchin. The discovery of the reduction division, for both the sperm and the egg in animals, was made by the Belgian biologist van Beneden, in 1883.

Fertilization serves two functions first, it initiates embryonic development, second, it is the means of uniting two diverse streams of heredity, with all the possibilities of new and favorable combinations of genes that this entails Because of its possibilities in the origination of something new and superior to that possessed by either parent, as well as something deleterious not shown by either, it is of supreme significance to the student of heredity

There can be little doubt that the facility with which new combinations of genes can be produced by meiosis and fertilization has been a leading factor in the evolution of the higher plants and animals in which this form of reproduction is so nearly universal.

CHROMOSOMES AND INDEPENDENT ASSORTMENT

At the first division of meiosis, as the chromosomes line up on the metaphase plate, it is purely a matter of chance whether one member of a chromosome pair faces toward a given pole of the cell or toward the opposite pole Furthermore, the orientation of one pair of chromosomes is not affected by that of another pair Since orientations may take place in all possible combinations, meiosis becomes a mechanism perfectly adapted to accomplish the independent assortment of gene pairs lying on separate chromosomes The relation between chromosome alignment and independent assortment in an organism having two pairs of chromosomes is shown diagrammatically in Fig 26 It is apparent that the chromosomes may orient themselves for the reduction division in one of two

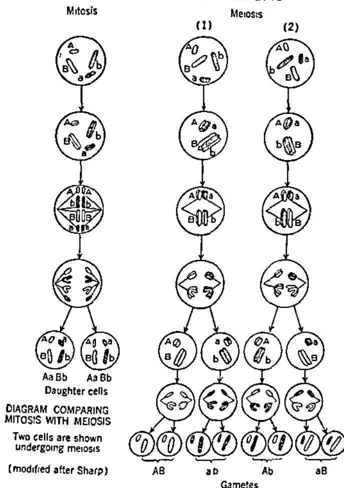


Figure 26. Diagram comparing mitosis with meiosis in an organism having two pairs of chromosomes The chromosomes derived from one parental gamete are indicated by stippling; those derived from the other are unshaded Two cells are shown undergoing meiosis, resulting in gametes of four types with respect to possible combinations of paternal and maternal chromosomes. (*Modified after Sharp, "Introduction to Cytology," McGraw-Hill Book Company, Inc.*)

possible ways (1 or 2) The result is four possible combinations in the gametes.

As already mentioned, the number of chromosomes is normally constant for each species, but varies among species. This variation is well illustrated in Table 5, a list which has been compiled from several sources, showing the chromosome numbers from familiar plants and animals Note

that the organisms are arranged to show a continuous numerical series, with a species to illustrate every chromosome number from the smallest possible (one pair) up to a fairly large one. Nearly all possible numbers up to 50 pairs have been reported, with scattered cases above 50 pairs The highest numbers have been found in certain plants, crustaceans, and insects Man, with 24 pairs, stands in the mid-region of the list. This number, incidentally, seems to be a very popular one: among other organisms that have 24 pairs are the chimpanzee, a species of bat, the European hedgehog, various species of wild mice, the water buffalo, the common potato, and ordinary tobacco

Numerous complex organisms, for example the Diptera (flies), have few chromosomes, while the equally complex Lepidoptera (butterflies and moths) have many Among the vertebrates chromosome numbers vary greatly In general, the cyclostomes, elasmobranchs, teleosts, and birds have large numbers, while lungfishes, amphibians (except certain urodeles), and reptiles (except the turtles) have small numbers—in these comparisons we are here considering man as near the average in chromosome number The mammals differ greatly in chromosome number: the egg-laying monotremes have many, the marsupials few, and the placental mammals vary from 16 pairs in one of the bats to 39 pairs in the dog On the whole the published lists show no obvious correlation between chromosome number and the complexity of the organism

Within a genus, as illustrated by *Drosophila* and *Carex*, chromosome numbers undoubtedly throw light on genetic relationships among the species Of the 215 species of *Drosophila* whose chromosome numbers are known, 86 species possess six pairs of chromosomes, 52 have five, 51 four, and 25 three, only one species has seven pairs [1] Fusions of the basic six pairs of chromosomes in various combinations have resulted in species with three, four, or five pairs According to one investigator,[2] in *Carex* the chromosome numbers range from 6 pairs to 56 pairs, with every number from 12 to 43 represented in one or more species. In this genus of plants, which consists of more than 1,000 species, the numbers 28, 42, and 56 occur with maximum frequency. Since these numbers are all multiples of 7 it is concluded that the basic number in the genus is seven pairs and that the higher multiples have come about by the duplication of entire chromosome sets—a process known as *polyploidy*, discussed in a later chapter Polyploidy is widespread in plants but relatively rare in animals. Intermediate numbers may arise by fusion or fractionation of individual chromosomes.

[1] J T. Patterson and W. S Stone, "Evolution in the Genus Drosophila," The Macmillan Company, New York, 1952

[2] H. A. Wahl, Chromosome Numbers and Meiosis in the Genus Carex, *Am J Botany*, 27:458–470, 1940.

TABLE 5 CHROMOSOME NUMBERS IN COMMON PLANTS AND ANIMALS*
(The total number of chromosomes in a body cell in each species is found by multiplying the number in the table by 2)

Common name	Scientific name	Pairs of chromosomes (haploid no , n)
Intestinal worm	*Ascaris megalocephala*	1
Small crustacean	*Cyclops viridis*	2
Fruit fly	*Drosophila willistoni*	3
Fruit fly	*Drosophila melanogaster*	4
Fruit fly	*Drosophila obscura*	5
Fruit fly	*Drosophila virilis*	6
Pea	*Pisum sativum*	7
Onion	*Allium cepa*	8
Primrose	*Primula sinensis*	9
Corn,	*Zea mays*	10
Opossum	*Didelphis virginiana*	11
Tomato	*Lycopersicon esculentum*	12
Bullfrog	*Rana catesbiana*	13
Salamander	*Ambystoma tigrinum*	14
Beetle	*Tribolbda canadense*	15
Bat	*Plecotus auritus*	16
Lizard	*Anolis carolinensis*	17
Minnow	*Fundulus heteroclitus*	18
Cat	*Felis domestica*	19
Mouse	*Mus musculus*	20
Rat (albino)	*Rattus norvegicus*	21
Cottontail rabbit	*Sylvilagus floridanus*	22
Guppy	*Lebistes reticulatus*	23
Man,	*Homo sapiens*	24
Meadow mouse	*Microtus townsendii*	25
Wood rat	*Neotoma floridanus*	26
Monkey	*Cebus, sp*	27
Silkworm moth	*Bombyx mori*	28
Moth	*Pygaera curtula*	29
Cow	*Bos taurus*	30
Gypsy moth	*Lymantria dispar*	31
Guinea pig	*Cavia cobaya*	32
Horse	*Equus caballus*	33
Gull	*Larus argentatus*	34
Camel	*Camelus dromedarius*	35
Sedge	*Carex riparia*	36
Sedge	*Carex aquatilis*	37
Sedge	*Carex rostrata*	38
Dog	*Canis familiaris*	39
Domesticated duck	*Anas platyrhyncha*	40
Fern	*Dryopteris abbreviata*	41
Crayfish	*Cambarus virilis*	100
Fern	*Dryopteris cristata*	164
Fern	*Ophioglossum vulgatum*	256

* For very extensive lists of chromosome numbers see C D Darlington and E. K Janaki Ammal, "Chromosome Atlas of Cultivated Plants," George Allen & Unwin, Ltd , London, 1945, and Sajiro Makino, "An Atlas of the Chromosome Numbers in Animals," Iowa State College Press, Ames, Iowa, 1951 The former book lists chromosome numbers for about 10,000 species of plants, the latter gives numbers for 2,754 species of invertebrates and 563 species of vertebrates

In no case do we know how many genes any organism possesses, but in the higher plants and animals the total must be very great In the common fruit fly, *Drosophila melanogaster*, which has been studied more intensively than any other organism, the number of genes has been estimated by various investigators at several thousand. In this fly there are only four pairs of chromosomes It follows that many genes must be found on one chromosome

In peas there are seven pairs of chromosomes, as shown diagrammatically in Fig 27 Here each gene of the seven characters studied by Mendel is represented on a separate chromosome It is obvious that if independent assortment is to take place at the reduction division, each gene must be on a separate chromosome, for if two genes were on the same chromosome, wherever one went the other would necessarily go, and there would be no independent assortment between them Mendel reported that his seven pairs of characters assorted independently. If true, this indicates that each gene was on a separate chromosome From Mendel's statement in his paper, however, it is not certain that he obtained progeny from every possible combination among his seven pairs of characters after he had obtained all of these combinations by crossing Without breeding all of the combinations it could not be proved that independent assortment existed among all seven Mendel's own statement on this point follows "In addition, further experiments were made with a smaller number of experimental plants in which the remaining characters by two's and three's were united as hybrids, all yielded approximately the same results " It seems improbable, however, that one with Mendel's good statistical sense would have failed to produce offspring from all possible combinations of hybrids It is significant that since Mendel's time no other experimenter with peas has found that any of the seven characters described by Mendel fails to assort independently of the other six. Hence these may be represented by genes on seven different chromosomes

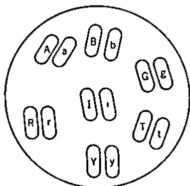


Figure 27. Diagram showing a cell of the pea, hybrid with respect to all seven of the characteristics studied by Mendel Each of the seven pairs of chromosomes is represented as carrying a different pair of genes

It must have been purely by chance that Mendel selected exactly the same number of contrasting characters as there were chromosomes in his plant, since there is no indication that he knew of the existence of chromosomes. A much more remarkable coincidence was his selection of seven characters whose genes were, presumably, all on separate chromosomes,

for, as can be shown by applying the law of probability developed in Chap. 2, if all of the genes in peas are distributed equally on the seven pairs and if we select at random seven genes, only one time in 163 will each of the seven be found on a separate chromosome.

Chromosomes and Independent Assortment in Man

All plants and animals that have been bred extensively show independent assortment. There is no reason to think that man is an exception to the rule. But the presentation of actual cases in man showing numerical ratios among the offspring (9:3:3:1, etc.), as the theory demands, is not easy. This is owing to the peculiar difficulties attending the study of human heredity. In man we are limited to the observation of matings already made, and it is hard to find an adequate number of pedigrees of the right sort for critical study. Casual observation of human families, however, reveals facts consistent with independent assortment in man. In large families it is usual to find the children displaying all sorts of combinations of characteristics found in the parents, grandparents, and more remote ancestors. For example, a child may show the ear shape of one parent, the eye color of the other, the hair form of a grandparent, and so on. Characteristics which are known to be Mendelian seem in many cases to be dealt out at random to the children.

No two human individuals have ever been found who are really alike in all respects (with the exception of identical twins, identical triplets, etc., discussed in a later chapter), and we can see now why the chance of two such individuals existing is so remote as to be practically impossible. Modern man, in most localities in countries such as ours, does not inbreed extensively; instead, wide crossbreeding is the general rule. As a consequence, in comparison with our domesticated animals, man is not purebred. The number of genes in which the average person is heterozygous is probably great.

In order to illustrate the effect of random assortment in producing variation among people, let us suppose that in each of his 24 pairs of chromosomes an individual parent is heterozygous with respect to one pair of genes. Using letters to stand for genes, as heretofore, we will represent his genetic constitution with 24 pairs of letters as follows: *AaBbCcDdEeFfGgHhIiJjKkLlMmNnOoPpQqRrSsTtUuVvWwXx*. Since each pair of genes in the assumed case is on a separate chromosome there will be independent assortment among all of them. We can readily calculate the number of kinds of eggs or sperms such an individual will produce by applying the principle already considered in Chap. 3. We have seen that with an individual heterozygous for one pair of genes (*Aa*) two kinds of eggs or sperms are produced; with an individual heterozygous for two pairs of genes (*AaBb*) four kinds are produced, with one heterozygous for

three pairs of genes ($AaBbCc$) eight kinds are produced, etc. Each time a pair is added the number of kinds of eggs or sperms is doubled, as shown in Table 6 The number with 24 pairs of genes is therefore 2^{24}.

The eggs or sperms produced by such a person will accordingly be a sample from 16,777,216 kinds Assuming for the sake of the example that the other partner in marriage is heterozygous for the same 24 pairs of genes (a highly improbable assumption), he or she likewise will produce a similar diverse array of gametes. At fertilization the possible different combinations of these genes will reach the enormous total of 282,429,536,481 This number is easily calculated by applying the rule that with one pair of genes there are 3 genotypes, with two pairs 9 genotypes, with three pairs 27 genotypes, with 24 pairs 3^{24} genotypes, and so on The actual number of visible types will depend upon the presence or absence of dominance in the various gene pairs and upon the interac-

TABLE 6

Pairs of genes	*Kinds of eggs or sperms*	*Pairs of genes*	*Kinds of eggs or sperms*
1	2	13	8,192
2	4	14	16,384
3	8	15	32,768
4	16	16	65,536
5	32	17	131,072
6	64	18	262,144
7	128	19	524,288
8	256	20	1,048,576
9	512	21	2,097,152
10	1,024	22	4,194,304
11	2,048	23	8,388,608
12	4,096	24	16,777,216

tion taking place among the genes The question of the interaction of genes is considered in the next chapter With complete dominance in all 24, the maximum number of visible types will be 16,777,216, since with complete dominance the maximum number of visible types in matings such as the one we are considering is exactly the same as the number of kinds of eggs or sperms With dominance present for some genes and lacking for others, the maximum number of visible types lies somewhere between the number of genotypes and the number of visible types in cases of complete dominance. The exact number (which can be calculated) depends upon the proportion of genes showing dominance.

In the preceding example we have considered the consequences when only one pair of genes on each chromosome is heterozygous. But each chromosome in man (judging by the fact that the number of Mendelian traits is many times the number of chromosomes) may contain not merely one gene but many; and if such "linked" genes frequently change places

with their mates on the other chromosome of the pair—as they are known to do in lower animals—the possible number of kinds of eggs and sperms is much greater than indicated in the preceding paragraph Hence the number of possible genotypes is correspondingly greater (The mechanism of exchange of genes is discussed in a later chapter under the head of crossing over.)

From the foregoing it is evident that the gene-chromosome mechanism is admirably adapted to produce an almost infinite variety of offspring It seems probable that among all the billions of human beings who have been born since man first appeared on the earth, there have never been two with identical sets of genes, unless they happened to develop from a single fertilized egg, as occurs regularly in identical twins, identical triplets, and so forth.

PROBLEMS

Note The subject of this chapter is the *physical basis of heredity*—the *chromosomes* An understanding of the behavior of the chromosomes during cell division enables us to visualize the laws of segregation and independent assortment Mendel's laws were discovered without a knowledge of the chromosomes From a study of chromosomes we now see that plants and animals have an internal mechanism which automatically produces results like those observed by Mendel This confirmation of the laws from an entirely different class of facts is in itself important But there is another reason for introducing a chapter on the physical basis of heredity at this point we shall need the knowledge thus gained in order to advance successfully to a supplementary principle discovered since Mendel's time—the principle of *linkage and crossing over*, considered in Chap 8

A thorough understanding of the processes of mitosis and meiosis is of special value in the study of heredity After you have read the descriptions and studied the illustrations of these processes, close the book and draw from memory a series of diagrams showing the stages of mitosis and meiosis in chronological order Learning the names of the cellular structures is important, because the structures will be referred to again and again in future chapters Names, however, are of secondary importance compared to a thorough grasp of the living processes and an appreciation of the significance of the processes

1 In many animals an unfertilized egg carrying only a *single set* of chromosomes may develop into a mature individual, but if in a fertilized egg one *pair* of chromosomes is missing the individual will not develop How can these facts be explained?

2. How can one account for the fact that in *Drosophila* and *Carex* there are continuous series of chromosome numbers?

3 Make a list of all the parental dihybrid combinations which Mendel would have had to produce, using his seven characters in peas, in order to demonstrate independent assortment among all seven characters

4. In peas, with seven pairs of chromosomes, show the method of calculating the chance that seven genes chosen at random will each be on a different chromosome, i e, that there will be no linkage

5. In corn there are 10 pairs of chromosomes What is the chance that any two genes chosen at random will be on the same chromosome, assuming that the genes are as likely to be on one chromosome as another?

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3. Make a list of all the parental dihybrid combinations which Mendel would have had to produce, using his seven characters in peas, in order to demonstrate independent assortment among all seven characters

4. In peas, with seven pairs of chromosomes, show the method of calculating the chance that seven genes chosen at random will each be on a different chromosome, i e, that there will be no linkage

5. In corn there are 10 pairs of chromosomes What is the chance that any two genes chosen at random will be on the same chromosome, assuming that the genes are as likely to be on one chromosome as another?

6. In man, brown eyes are dominant over blue In the *Journal of Heredity*, 1951, Isadore Ludwin describes a family in which a woman has one brown eye and one blue eye Her mother is brown-eyed and her father is blue-eyed Her husband is blue-eyed, and of their 13 children 6 are brown-eyed and 7 blue-eyed List the possible explanations of the woman's heterochromia iridis, as this condition is called.

7. Why is a sperm alone not able to develop into an individual, while eggs of numerous species of plants and animals are able to develop parthenogenetically without fertilization?

8. List the functions of meiosis

9. What is the function of mitosis?

6

THE FACTOR PRINCIPLE: ACTION AND INTERACTION OF GENES

In the examples of Mendelian heredity considered thus far each character was "determined" by a single gene Such characters have often been called unit characters because the change in a single gene completely changes the character Not long, however, after the rediscovery of Men-

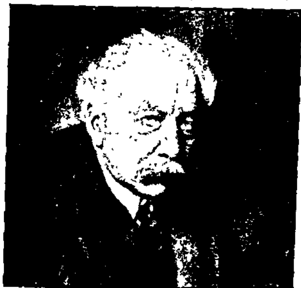


Figure 28. William Bateson, 1861-1926 *(Courtesy of Prof R C Punnett.)*

del's paper in 1900, investigators began to report experiments that did not fit this simple scheme Ratios diverging widely from simple Mendelian ratios were sometimes obtained As a matter of fact Mendel himself had described briefly such a case in beans. We shall return to this case presently.

The first reported experiments, following Mendel's, showing such

unusual ratios were made by the British biologists W. Bateson and R. C. Punnett. Bateson was one of the leaders in the study of heredity and variation during the latter part of the nineteenth century. He was among the first to recognize the importance of Mendel's work and in 1902 published the first English translation of the paper on peas. Bateson and Punnett's earliest case dealt with the heredity of comb shape in chickens. Another one of their early experiments concerned the color of sweet peas. Since the sweet pea case illustrates perfectly the principle of two or more genes acting upon a single character, it will be used as our first example.

COLOR IN SWEET PEAS

There are many pure-breeding varieties of sweet peas, all supposedly derived from the wild pea of Sicily, which has purple flowers. While investigating the heredity of flower color in these plants Bateson and Punnett found that red was inherited as a simple dominant, white being recessive.

In one experiment they crossed two different white-flowered plants and were surprised to find that the resulting hybrids had red flowers. When these hybrid red plants were allowed to self-fertilize, they produced red flowers and white flowers in the ratio of 9 red: 7 white.

The explanation of this wholly unexpected result is as follows. The red color requires for its development the combined influence of two separate dominant genes which we may designate as *R* and *C*. A change either of *R* to *r* or *C* to *c* prevents the development of red pigment and thus causes the plant to be white. The two white plants used in the original cross were genetically different: one was *rrCC* and the other *RRcc*. As long as each was bred by itself it remained constant, but when the two were crossed each brought in a different dominant gene, *R* and *C* respectively, both of which were necessary for the production of red pigment. Red pigment accordingly developed in the hybrid *RrCc*.

When the red hybrids self-fertilize, their genes sort out and recombine independently in all possible combinations, as indicated in the checkerboard (Fig. 29), exactly as in cases of independent assortment previously described (Chap. 3). The only difference between this case and independent assortment in Mendel's experiments with edible peas is that in sweet peas both pairs of genes produce their effect on one and the same characteristic, namely, color. The mechanism of *distribution* of the genes is exactly the same. Obviously, we are here dealing with nothing contradictory to Mendel's laws, but with a new principle supplementary thereto. Furthermore, this result in sweet peas is just what one might have expected from what we know of the nature of chemical reactions in general. A specific chemical reaction, such as the production of a pig-

ment, might be expected to require two different substances, one substance depending upon the presence of one gene and another substance depending upon another gene.

An inspection of the checkerboard reveals that there are three whites due to the presence of *rr*, three due to *cc*, and one due to the presence of

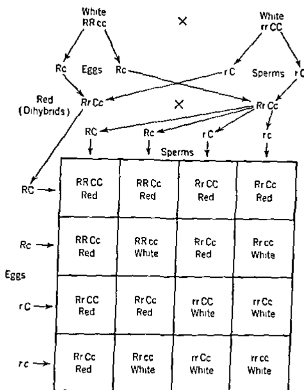


Figure 29. Diagram showing the production of red sweet peas from a cross between two varieties of white sweet peas and the production of 9 reds to 7 whites as offspring of the hybrids

both (*rrcc*) in the same individual These seven whites are visibly indistinguishable, with the result that the visible ratio is 9 red · 7 white.

Problems of this kind may also be easily solved by means of the fractional method, thus:

F_1 Dihybrid *RrCc*

F_2 Phenotypes (using roman letters for phenotypes)

$\frac{3}{4}$ R $\frac{3}{4}$ C = $\frac{9}{16}$ R C} Red $\frac{9}{16}$

$\frac{3}{4}$ R · $\frac{1}{4}$ c = $\frac{3}{16}$ R c

$\frac{1}{4}$ r $\frac{3}{4}$ C = $\frac{3}{16}$ r C} White $\frac{7}{16}$

This example illustrates perfectly the fact that the gene rather than the character is the unit of heredity. We can now see that a difference between two contrasting characters may rest upon a single gene difference, as in Mendel's seven characters in peas, or upon two or more gene differences, as in color in sweet peas It is therefore best to avoid the use of the term unit character. The appearance of the red color in sweet peas is obviously dependent upon two different genes, *R* and *C* (incidentally, known to be located in separate chromosomes, since they assort independently) It is therefore incorrect to say that red is "determined" by either one or the other The genes *R* and *C* are merely *factors* whose combined effect is pigment formation

In succeeding years many other examples involving the factor principle, similar to that of the sweet peas just described, have been discovered both in plants and animals. In corn, for example, the colors red and white are inherited in exactly the same way as red and white in peas Several other examples will be given presently.

The discovery of the factor principle has served to clear up a longstanding puzzle which goes under the name of reversion, or atavism. These terms are applied to all those cases in which an individual suddenly appears that differs from its parents, but resembles some more distant ancestor Before the discovery of Mendel's laws such "throwbacks" could not be satisfactorily explained, but now we see how simply they fall into order merely by assuming that each parent comes from a distinct hereditary line in each of which there is present some gene or genes lacking in the other In matings between the two lines, the long-separated genes recombine and restore the character which may have disappeared countless generations previously.

MENDEL'S CASE IN BEANS; QUANTITATIVE INHERITANCE

As already mentioned, Mendel found a case that he thought illustrated the interaction of two pairs of genes This involved the color of the flower in beans. In a cross between a white-flowered plant and a purple-flowered plant the hybrids resembled the purple parent in color, though the color was of less intensity. Dominance was incomplete, in this respect differing from the sweet pea case we have just considered.

Unfortunately, but as was to be expected from a species hybrid, the F_1's were not very fertile. From 17 plants, which together developed many hundreds of flowers, only 49 seeds in all were obtained The following year only 44 F_2 plants were raised from these seeds and of these only 31 reached the flowering stage; one of the 31 produced white flowers, the other 30 developed a series of flower colors ranging from purple to

pale violet These F_2 plants likewise were not fully fertile, some were sterile, and only 15 plants produced well-developed seeds

The experiment was continued through two more generations, with similar unfavorable results as to fertility Some of the plants that had violet flowers bred true, while the majority of this color produced both violet-flowered and white-flowered offspring This indicated that some of the violet-flowered plants were homozygous and others were heterozygous.

Since the various colors in this experiment depended upon the amount of pigment, the case is an example of *quantitative inheritance*

Mendel realized that his numbers were insufficient to establish a law, but suggested as an hypothesis that the purple-red color was the resultant of two or more independent factors which may be designated as *A* and *B* (simplifying slightly Mendel's symbols) He pointed out that if white depended upon two independent recessive factors, which we will call *a* and *b*, only one white would be expected out of 16 offspring of the dihybrid; and since, as we have seen, a dihybrid produces nine genotypes, the remaining $^{15}/_{16}$ of the offspring should fall into a series of eight colors corresponding to the remaining eight genotypes, as follows *AABB* (purple-red), *AABb, AaBB, AAbb, AaBb, aaBB, Aabb, aaBb* (seven shades of violet). Mendel does not say how many color grades he actually observed, but obviously his hypothesis of eight grades of colored flowers would hold true only in case of lack of dominance in both pairs of genes, and only when there is a visibly distinguishable effect of *A* and *B* in all eight combinations as listed above

To show how this color variability would work out, let us go a step beyond Mendel and arbitrarily assign numbers For instance, let 6 represent the grade of color produced by the gene *A*, and 4 the grade of color produced by *B*. We will also assume that these effects are additive in all combinations Substituting the numbers for letters in the above series of nine genotypes, we get the following results

Color grade	20	16	14	12	10	8	6	4	0
Genotypes	*AABB*	*AABb*	*AaBB*	*AAbb*	*AaBb*	*aaBB*	*Aabb*	*aaBb*	*aabb*
Ratio	1	2	2	1	4	1	2	2	1
Colors	Purple-red	Various shades of violet							White

Mendel thought enough of his hypothesis to suggest that it would be "well worth while to follow up the development of color in hybrids by similar experiments, since it is probable that in this way we might learn the significance of the extraordinary variety in the coloring of our ornamental flowers."

THE FACTOR PRINCIPLE APPLIED TO MAN; CONTINUOUS VARIATION

Skin color in man apparently follows a rule similar to that suggested by Mendel for flower color in beans. According to Davenport,[1] who made extensive observations of Negro-white crosses and the descendants of the mulattoes resulting from such crosses, in Jamaica, the difference in the amount of black pigment between the Negroes native to West Africa and Europeans rests upon two major pairs of genes. This theory is accepted in general by Gates,[2] as in harmony with his findings in numerous Negro × white pedigrees Gates points out that there are important gene differences among Europeans respecting skin color Among some whites a gene for dark pigmentation seems to be dominant over the gene for fair skin This must be taken into account in studying Negro-white pedigrees; accordingly, Gates proposes a three-factor explanation as better fitting the facts than a two-factor theory.

From what is known of the inheritance of pigmentation in other mammals, as well as observations of the many varieties of skin color in man, it is probable that there are numerous genes having minor effects in addition to a few with major effects We have every reason to believe that segregation and assortment of genes for pigmentation occur in man as in other mammals, but owing to practical difficulties in the study of human heredity, the genes in man have not been identified with the certainty that is found in laboratory rodents. Here is an interesting field for further research in the genetics of man

A full-blooded Negro, according to Davenport, may be represented by *AABB* and a Caucasian by *aabb*. Dominance is lacking, the hybrid being intermediate in color Each pair of genes segregates independently so that all possible combinations occur in the offspring of the hybrids Davenport concluded that each gene mentioned was responsible for approximately the following proportion of black *A* 19 per cent, *B* 16 per cent, *a* 2 per cent, *b* 1 per cent The full-blooded Negro (*AABB*) is therefore 70 per cent black in color and the Caucasian 6 per cent black; the full color in each race is due to a mixture of black and yellow pigments plus red from the blood, diluted with the natural white color of unpigmented skin. The hybrid, or mulatto (*AaBb*), is 38 per cent black.

The children of two such hybrids will therefore represent a series of colors in which the expected ratio, with the percentage of black in each class, is as follows 1 (70 per cent).2 (55 per cent):2 (53 per cent).1 (40 per cent)·4 (38 per cent).1 (36 per cent).2 (23 per cent):2 (21 per

[1] C. B Davenport, Heredity of Skin Color in Negro-White Crosses, *Carnegie Inst Wash*, *Publ* 188, 1913

[2] R. Ruggles Gates, "Pedigrees of Negro Families," Blakiston Division, McGraw-Hill Book Company, Inc, New York, 1949

cent):1 (6 per cent). It is noted that one out of 16 should be as dark as the full-blooded Negro grandparent, and that one out of 16 should be as light as the white grandparent The other 14 will be intermediate (four the same shade as the hybrid parents, two others nearly the same, four considerably darker, and four considerably lighter) The visibly distinguishable ratio, therefore, might be 1 4 6 4 1 among the offspring of the F_1's of Negro-white crosses

If we allow for the effects of minor color genes and for the effect of sunlight in stimulating pigment formation, a much larger number of color varieties might appear There might, in fact, be found practically a continuous range of colors from black to white Given a sufficient number of genes affecting a character, the mechanism of segregation and assortment can account for the observed continuous variability in numerous quantitative characters, such as the skin color in man.

It should be pointed out, however, that the foregoing facts do not imply that either a pure Caucasian or a pure Negro is likely to result from a mating of two mulattoes The chance of this happening is extremely remote, since there are many differences between the two races other than skin color-- shape of nose, thickness of lips, hair form, numerous minor skeletal differences, etc —each depending upon gene differences It is not likely with so many genes involved that these will be recombined in exactly the same manner as in either of the two original races. Occasionally, however, a child from hybrid parents might receive the proper assortment of genes to enable it to pass as an unmixed member of one race or the other

If the ancestry of the parents is of less than one-half Negro the chance of a child's being Caucasoid in type is increased. Gates gives an illustrated pedigree of such a case This pedigree also shows that it is possible for a child of mixed parents to be darker than either parent The belief of some that two light-skinned parents, one of whom is of mixed Negro-white ancestry, may produce a "black" child is, however, unsupported by the facts. This belief may go back to Aristotle's ambiguous statement in the *Generation of Animals:* "There was a woman in Elis who had intercourse with a blackamoor, her daughter was not a black, but that daughter's son was."

INTERACTION OF GENES IN GUINEA PIGS

Guinea pigs offer a striking example of the interaction of several genes in the production of hair and eye color in mammals The case will be presented in some detail because the principles involved have a broad application. The wild rodent of South America from which the guinea pig was derived is colored somewhat like the North American red squir-

rel When examined closely each hair is seen to be dull black at the base, with a reddish band near the tip, and with a black tip This banding of the individual hairs is known as *agouti*, named after another South American rodent (the agouti), which shows the same pattern to a pronounced degree The pattern is common also in North American rodents such as rats, mice, woodchucks, and squirrels, as well as in some other mammals, including raccoons, rabbits, cats, and foxes The color of the band varies in different mammals, ranging from red through yellow and cream to white. There is often more than one band in a single hair, especially if the hair is long. The writer has counted as many as three distinct reddish bands in the long tail hairs of a fox squirrel

The agouti pattern is probably an advantage to many wild animals in that it tends to give them a neutral color which blends with their environment, thus affording protection against enemies. Anyone who has observed wild rabbits in the field can vouch for the concealing effect of their coloration. In the case of predatory animals it may be an advantage in enabling them to approach the prey without detection.

In guinea pigs the agouti is a common color variety, but like all animals that have been under domestication for centuries, the guinea pig shows many color variations, including solid black, sepia, white, chocolate brown, red, yellow, black and white spotted, black and red spotted, black-red-white spotted, and so on The guinea pig is thought to have been domesticated from the wild Peruvian cavy (*Cavia cutleri*). At the time the Spaniards first visited Peru they found Indians raising guinea pigs for food, a practice which is still followed

The individual colors in the guinea pig are not very different from those found in the hair of man, but in man spotting is rare, with the exception of dark and white spotting The numerous color variations of domesticated guinea pigs undoubtedly came either from the wild type or from other color varieties by sudden mutations occurring from time to time In nature most of these colors would be disadvantageous to their possessor by making it more conspicuous and a ready prey to predatory animals This fact explains the scarcity of such colors among wild animals

The heredity of the color varieties of the guinea pig has been studied by many investigators, and most exhaustively by Professor Sewall Wright In all known cases in guinea pigs the color mutations from the wild type are inherited as recessives Among the best known of these mutations are those shown in the table on page 91.

As regards color, the wild-type guinea pig therefore has the gene formula *SSEEAACCBBPP* Each one of these genes is necessary for the production of the typical wild color pattern. By a long continued process of crossing guinea pigs possessing the alternative recessive mutations, Wright succeeded in building up a family of animals combining all six

recessive genes, *sseeaaccbbpp*. In appearance they are pale brown, yellow spotted, white spotted, without agouti bands, and with pink eyes He then crossed these multiple recessives with the wild type The hybrids were like the wild type (except that in some there was a trace of white spotting, as expected from the fact that *S* is not always dominant over *s*) The genetic formula of the hybrids was of course *SsEeAaCcBbPp*.

Dominant	*Recessive*
SS, No white spots (Dominance irregular)	*ss*, White spots
(*S* and *s* are so nicely balanced in their effect that the amount and pattern of the white areas is quite variable Sometimes *S* behaves as a complete dominant, rather more frequently the hybrid (*Ss*) has a little white on nose and feet)	
EE, No red spots	*ee*, Red spots* (size and pattern of red spots variable)
AA, Agouti pattern	*aa*, No agouti bands
CC, Intense color	*cc*, Red reduced to yellow, black slightly reduced*
BB, Black eyes, black hair	*bb*, Brown eyes, brown hair, red unaffected
PP, Dark eyes, dark hair	*pp*, Pink eyes, pale-sepia or pale-brown hair, red unaffected

* In order to distinguish them from other genes in a series of alleles Wright uses the symbol e^p to represent the gene for red spotting and c^k for the gene *c* above For the sake of simplicity I have dropped these superscripts in the present discussion

The hybrids were then backcrossed to the multiple recessives [1] As we have seen (Table 6, page 80), hybrids in six respects should produce 64 kinds of eggs and sperms. These 64 kinds should of course occur in equal numbers provided all six genes are on separate chromosomes In Table 7 in the left-hand column are listed all the possible combinations (32 in number), omitting the gene for white spotting By combining these 32 with *S* and *s*, respectively, shown in the two right-hand columns, we get 64 combinations Upon fertilization, the union of these 64 kinds of eggs and sperms with eggs or sperms from the multiple recessive (all of which are *seacbp*) results in 64 gene combinations, or genotypes

Note in Table 7 under Visibly distinct types that in four instances two genotypes must be lumped together because genes *C* and *c* have practically the same effect upon black and brown The consequent lumping reduces the number of visibly distinct types to 56, all of which were actually obtained by Wright among the 399 offspring produced by the backcross matings The numbers of each type he obtained are shown in the two right-hand columns of Table 7. With a perfect distribution of the 399 offspring among the 56 types there should be approximately six of each

[1] Sewall Wright, An Eight-factor Cross in the Guinea Pig, *Genetics*, **13** 508–531, 1928 In this experiment two genes affecting hair direction (roughness) also were studied.

TABLE 7 OFFSPRING FROM A SIX-FACTOR BACKCROSS IN THE GUINEA PIG*
($SsEeAaCcBbPp$) × ($sseeaaccbbpp$)

Genotypes	Visibly distinct types	Offspring: Little or no white (Ss)	Offspring: White spotted (ss)
e a c b p (eggs and sperms of recessives)			
× (Eggs and sperms of hybrids)			
E A C B P	Black, red agouti	9	5
E A c B P	Black, yellow agouti	10	7
E A C b P	Brown, red agouti	4	7
E A c b P	Brown, yellow agouti	6	5
E a C B P	Black }	12	16
E a c B P	Black }		
E a C b P	Brown }	18	10
E a c b P	Brown }		
e A C B P	Black, red agouti, red spots	4	8
e A c B P	Black, yellow agouti, yellow spots	6	7
e A C b P	Brown, red agouti, red spots	6	4
e A c b P	Brown, yellow agouti, yellow spots	9	7
e a C B P	Black, red spots	12	1
e a c B P	Black, yellow spots	2	5
e a C b P	Brown, red spots	9	5
e a c b P	Brown, yellow spots	5	5
E A C B p	Pale sepia, red agouti	9	6
E A c B p	Pale sepia, yellow agouti	6	6
E A C b p	Pale brown, red agouti	6	7
E A c b p	Pale brown, yellow agouti	3	10
E a C B p	Pale sepia }	12	17
E a c B p	Pale sepia }		
E a C b p	Pale brown }	18	17
E a c b p	Pale brown }		
e A C B p	Pale sepia, red agouti, red spots	5	8
e A c B p	Pale sepia, yellow agouti, yellow spots	5	3
e A C b p	Pale brown, red agouti, red spots	5	5
e A c b p	Pale brown, yellow agouti, yellow spots	5	3
e a C B p	Pale sepia, red spots	8	7
e a c B p	Pale sepia, yellow spots	5	6
e a C b p	Pale brown, red spots	3	1
e a c b p	Pale brown, yellow spots	2	7
Total	. . . .	204	195

* After Wright

type, except in the four groups which are lumped, in these there should be approximately 12. The numbers actually obtained are as near to this ratio as could be expected with so large a number of types and only 399 individuals By various statistical tests Wright shows that the results clearly indicate independent assortment among all six genes studied This means that each of the six genes is located on a different chromosome This is not a surprising result in view of the fact that the guinea pig has 32 pairs of chromosomes

No experiment could serve better than the one just described to show that the color of an animal is not a unit character, but that the gene is the unit. Note, for example, that the pale-brown pink-eyed animals (*SsEeaaCcbbpp*) resulting from *seacbp* × *SEaCbp* have pale-brown color because of the cooperation of the three pairs of recessive genes *aa*, *bb*, *pp* The pair *aa* eliminates the agouti band from the hair, the pair *bb* changes the quality of the pigment from black to chocolate brown, and *pp* reduces the intensity of the brown to a pale brown

AN EXAMPLE OF REVERSION, OR ATAVISM, IN THE GUINEA PIG

In his comprehensive work "The Variation of Animals and Plants under Domestication," first published in 1868, Darwin has a long chapter on "Reversion or Atavism" (*atavus*, ancestor) These terms were used in pre-Mendelian days to denote the occasional resemblance of offspring to a grandparent or to some more remote ancestor, in a character differing from that of the parents, for example, the sudden appearance of a gray, or black, or black-spotted lamb in a flock of sheep of a breed that ordinarily produces only white sheep was known as a reversion—the wild color of domesticated sheep was thought to have been "brown or dingy black." Today we know that the black color in sheep is inherited as a Mendelian recessive

Darwin shows clearly that he had not read Mendel's paper He refers repeatedly to the work of the plant hybridizer Naudin, a French contemporary, who in 1865 came close to stating the law of segregation In the end, however, Darwin's explanation, like that of Naudin's, is incomplete and unclear because it lacked the concepts of purity of the gene and the precise quantitative relationships of segregating and combining gametes, as developed by Mendel

In Fig 30 we have a photograph of a pair of adult guinea pigs and their litter of five, which Darwin would have regarded as a case of reversion Our present knowledge of the genes affecting hair color and eye color and of their interactions, as described in the preceding pages, however, enables us to account for the case in simple terms The litter of five black-haired, black-eyed guinea pigs was sired by the albino male shown with

them The dam, also shown, is pale sepia, pink-eyed, with no spotting. The genotype of the albino male is $s\text{–}e^r\text{–}a\text{–}c^ac^aP\text{–}B\text{–}$. (The dashes indicate uncertainty as to heterozygosis.) The symbol e^r is used for red spotting and c^a for albino An animal that is homozygous for gene c^a is an albino regardless of its other genes, the gene c^a is said to be *epistatic* with respect to other genes affecting color The female is of genotype $S\text{–}Ee^raaC\text{–}ppB\text{–}$.

Two of the young are self black Their genotype is $S\text{–}E\text{–}aaCc^aPpB\text{–}$. The *aa* accounts for non-agouti pattern, *C* ensures full intensity of pigmentation, *P* is the dominant alternative of the gene for pink eyes and



Figure 30 A litter of five black guinea pigs, their albino sire, and pink-eyed pale sepia dam. (*Photograph by the author*)

pale colors; and *B* works to produce black pigment rather than brown The albino sire supplied the dominant gene *P* which was lacking in the dam.

Of the other three young, two have each a white foot and one has a small amount of red spotting. Their genotypes are therefore like those of the two self blacks except for the substitution of *Ss* in the white-spotted animals and e^re^r in the red-spotted one.

One may ask how we know that the albino male carries the gene *B* The answer is that albino guinea pigs, like Siamese cats and Himalayan rabbits (Chap 11), develop some pigment on feet, nose, and ears when they are exposed to low temperatures This animal had been so exposed and had developed conspicuous black pigment in the regions mentioned

Had he been *bb* this pigment would have been brown in color and inconspicuous This same temperature effect enables us also to tell that he carries at least one gene *s* One of his feet remained white, indicating a white spot. in white-spotted areas no pigment develops, even at low temperatures.

MULTIPLE EFFECTS OF A SINGLE GENE, LETHAL GENES

Although the gene is the unit of heredity, a single gene often affects more than one characteristic of the organism, sometimes in wholly unexpected ways In chickens a well-known example of a gene with multiple effects is the gene C^r, known as *crest.* It is responsible for the long, partially erect feathers producing a distinct crest in breeds like the Silkies, Polish, and Houdan[1] (Fig. 31). These breeds belong to what are regarded as ornamental varieties, and the crest has been developed for its beauty by human selection over a period of centuries Examination discloses that the skull of crested birds is highly abnormal in many ways Darwin, who made a thorough study of the varieties of fowls, examined 14 skulls of Polish and other crested breeds and gave detailed descriptions of them[2] One of the most conspicuous features is the large hemispherical protuberance of the frontal bones, which include the cerebrum of the brain (Fig. 32). As can be seen in Fig 32, the frontal bones in the Polish skull are very thin as compared to the Cochin, and there are openings where no bone has formed. These open spaces are covered with membrane only Darwin found that the protuberance varied greatly in size and in the degree of ossification of the roof of the skull. Usually there were many variously shaped open spaces, the bone forming an irregular network. In one specimen there was no bone whatever over the whole protuberance, and the skull when viewed from above presented the appearance of an open basin As one might expect, the brain is modified in shape in a corresponding manner. Darwin investigated the question as to whether there was abnormality of behavior among these birds He found evidence that in some instances crested birds were stupid and abnormal in their reactions.

Other characteristics of the crested breeds are short beak, comb absent or small and of unusual shape, wattles either present or replaced by a beardlike tuft of feathers (Fig 31).

The basic cause of the abnormalities is an accumulation of fluid in the third and fourth ventricles of the brain, resulting in a protuberance of

[1] R. A. Fisher, Crest and Hernia in Fowls Due to a Single Gene without Dominance, *Science*, 80:288-289, 1934

[2] Charles Darwin, "The Variation of Animals and Plants under Domestication," 2d ed. 1875, D. Appleton & Company, Inc., New York, 1887.

the cerebral hemispheres and the overlying bones The skin on this protuberance is thickened

Darwin made no crosses between crested and noncrested breeds, although he did cross several other breeds of chickens During the early part of this century, however, several investigators made such matings



Figure 31. White Houdan male fowl; from a crested breed developed in France. Note well-developed crest, beard, and small V-shaped comb (*Courtesy of U S. Department of Agriculture*)

The most recent are those by Fisher, cited above, and Warren and Hutt[1] As a result of these studies it seems clear that the crest depends upon a single mutation A double dose of the mutant gene, C^rC^r, makes the skull so defective that the cerebrum pushes through, forming a cerebral hernia Homozygous birds usually die; heterozygous birds develop no hernia and

[1] D. C. Warren and F B Hutt, Linkage Relations of Crest, Dominant White, and Frizzling in the Fowl, *Am. Naturalist*, **70**:379–394, 1936

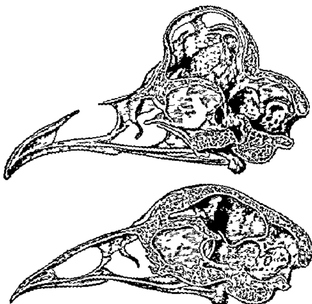


Figure 32 Longitudinal sections of skulls, natural size, lateral view, of two breeds of fowl *Top* Polish cock *Bottom* Cochin cock, selected for comparison with the above from being of nearly the same size (*From Charles Darwin, "The Variation of Animals and Plants under Domestication,"* D Appleton & Company, Inc, 1887)

are more or less normal From heterozygotes the breed is kept going Matings between heterozygous crested birds produce a ratio as follows:

1 C^cC^c Crest Cerebral hernia (Usually die)	2 C^cc^c Crest No hernia	1 c^cc^c No crest Brain normal

The gene C^c obviously behaves as a dominant with respect to crest With respect to skull and brain there is no dominance, the heterozygote is intermediate, although as to its lethal effect the gene is recessive.

The Yellow Mouse

In mammals we have an excellent example of a lethal gene with multiple effects, this is the gene A^y for yellow in mice Yellow is dominant to the agouti gene in mice It is impossible to obtain a pure-breeding strain of yellow mice: yellows always breed as heterozygotes. The yellow stock is kept alive either by mating yellow with yellow or by backcrossing yellow with nonyellow. The backcross mating yellow × nonyellow gives a

ratio of 1 yellow:1 nonyellow. A mating of yellow × yellow gives 2 yellows 1 nonyellow, instead of 3.1 as expected from a mating of heterozygotes The deficiency of yellows is here due to the prenatal death of the homozygous yellows.

Evidence for the lethal effect of gene A^y in double dose is found not only in the abnormal ratio just mentioned but from the examination of pregnant females. Operations on such females by several investigators, cited by Gruneberg,[1] have disclosed that approximately one-fourth of the

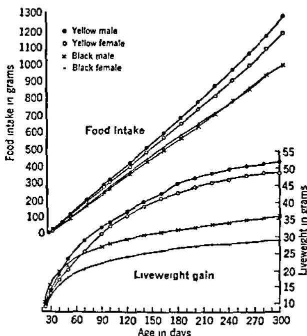


Figure 33. Curves showing average gain in weight and food consumption in mice for all sets of yellow and black littermates within each age and sex. *(From Dickerson and Gowen, Science, May 9, 1947)*

embryos die very early and disintegrate *in utero* It is concluded that these embryos are largely made up of homozygous yellows

The gene A^y has another important effect: yellow mice, especially the females, beginning at about 40 days of age, put on excess fat. This results from the slightly better appetites and the relative inactivity of the yellows From the increase in food intake and reduction in energy expended, the yellow mice continue to increase in weight so that by 300 days of age they may exceed their nonyellow littermates by 50 per cent in the males and 70 per cent in the females (Fig. 33). Dickerson and

[1] Hans Grüneberg, "The Genetics of the Mouse," 2d ed., Martinus Nijhoff, The Hague, Netherlands, 1952

Gowen[1] found from chemical analyses that the excess weight of the yellow mice was due entirely to fat tissue.

Besides its effect on coat color and fat storage and its lethal effect when homozygous, the gene A^y also shortens the reproductive period and the expectation of life of heterozygous females

When gene A^y is introduced into albino mice there is no effect on coat color: the gene for albinism is epistatic with respect to color However, such albino A^y mice develop obesity like yellow mice We could therefore just as well speak of A^y as the gene for obesity as the gene for yellow. For convenience one usually refers to a gene by its most conspicuous effect and ignores its other effects The yellow color is usually the most conspicuous effect of the gene A^y

Gruneberg states that "all genes in the mouse which have been studied with any care have *manifold* or '*pleiotropic*' effects which cut across any attempt to deal with the genes according to the organ mainly affected"

Phenylketonuria

In man we have an ideal example of a gene with multiple effects in the one responsible for the recessive disease or syndrome known as phenylketonuria. The name signifies the presence of substances called phenylketones in the urine The basic abnormality is the inability of the affected individual to metabolize the essential amino acid phenylalanine As a consequence, this amino acid is found in excessive quantities in the blood, cerebrospinal fluid, and urine The most important effect of this metabolic error is extreme mental defect

In his excellent book on mental defect,[2] Professor Penrose, of the Galton Laboratory, University College, London, discusses the condition at some length He notes that about 60 per cent of the cases are of the idiot grade and 30 per cent imbecile. Other symptoms that are frequently present, but not in themselves diagnostic, are reduction in stature and head measurements, widely spaced incisors, tendency to develop pigmented patches in the skin, dermatitis, excessive sweating, hunchback, accentuation of all reflexes, and digital mannerisms The gene also tends to reduce the amount of pigment in hair and eyes Biochemical studies indicate that the defectives lack some enzyme capable of metabolizing phenylalanine, resulting in a diminished rate of oxidation in the brain cells, deficiency of pigment formation, and a variety of other abnormalities The accumulation of the amino acid in the body fluids is the most certain diagnostic symptom (Fig 34). No permanent cure is known, although British investigators have reported that a special diet free from phenylalanine produces a marked increase in intelligence.

[1] G E Dickerson and J. W. Gowen, Hereditary Obesity and Efficient Food Utilization in Mice, *Science*, 105:496–498, 1947

[2] Lionel S Penrose, "The Biology of Mental Defect," Grune & Stratton, Inc , New York, 1949

Fortunately, the defect is rare—about one case in 25,000 to one in 50,000 among most Europeans and their descendants in the United States. According to Penrose, no phenylketonuric of Jewish origin has been discovered and none among American Negroes.

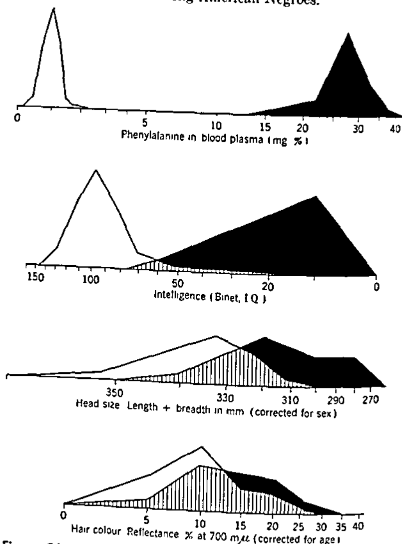


Figure 34. Histograms showing frequency distributions of four traits in phenylketonurics (*right*) compared with control population (*left*) (*From Penrose, Ann. Eugenics,* **16**:135, 1951)

The evidence all points to recessive inheritance· practically all cases come from normal parents (affected persons are highly infertile); the ratio of normals to defectives agrees with expectancy in families showing the trait; and as with other rare recessive traits, the percentage of cousin marriages is relatively high among the parents In a recent survey of

1,000 inmates of a state home for the feebleminded in Michigan,[1] nine cases were found In three instances there were two affected persons from the same family. The IQ's of the nine ranged from 6 to 34, all but one had spread incisors, in all but one the eyes were blue or blue-gray, and all showed exaggerated reflexes, as well as one or more of the other traits mentioned above. We thus have in this metabolic disorder an excellent example in man showing that a single gene can produce a variety of effects

Summarizing, as to the manifold effects of a single gene no clearer statement has been found than that of Professor Dobzhansky, of Columbia University, in his excellent book "Genetics and the Origin of Species,"[2] from which we quote

Mutant genes are named according to their most prominent characteristics In *Drosophila*, mutations of the gene "white" turn the eye color from red to white, "vestigial" makes vestigial wings, "stubboid" causes a shortening of the bristles, and so on This system of naming is convenient but the names are not to be taken as complete accounts of the differences between mutants and the ancestral form, much less as indicative of the total range of the effects of the particular gene on the development. Many mutants, in *Drosophila* as well as in other forms, differ from the ancestral types in complexes of characters The mutation white changes the eye color, that of the testicular membrane, the shape of the spermathecae, length of life, and general viability Vestigial reduces wing size, modifies the balancers, makes certain bristles erect instead of horizontal, changes wing muscles, shape of the spermathecae, speed of growth, fecundity, and length of life Under favorable external conditions vestigial relatively decreases the number of ovarioles in the ovaries while it has the opposite effect under unfavorable conditions Stubboid modifies the bristles, wings, legs, antennae, and viability

Genes that produce changes in more than one character are said to be pleiotropic or to have manifold effects The frequency of such genes is not well known A majority of mutations produce striking changes in a single character, and their manifold effects, if any, involve changes which appear trivial Thus, the main characteristic of the mutant vestigial in *Drosophila* is a decrease of the wing size But to conclude that vestigial is a "wing gene" rather than a "bristle gene" would be as naive as to suppose that a change in the hydrogen ion concentration is a "color gene" because it produces a striking change in the color of certain indicators

PROBLEMS

1 Show the ratios expected among the progenies of the following crosses in sweet peas·

a Red (*RrCc*) × white (*rrcc*)

b Red (*RRCc*) × white (*rrcc*)

[1] F. W Crowe and W J Schull, Phenylketonuria Studies in Pigment Formation, *Folia Hered et Pathol*, 1:259–268, 1952

[2] Theodosius Dobzhansky, "Genetics and the Origin of Species," 3d ed , p. 33, Columbia University Press, New York, 1951.

c Red (*RrCC*) × red (*RrCC*)
d White (*rrCc*) × white (*Rrcc*)

2. Assume that the difference in stature between two groups of people, one averaging 5 feet 4 inches in height and the other averaging 6 feet in height, depends upon two independent genes (*AABB* = 6 feet, *aabb* = 5 feet 4 inches) Assume also that there is no dominance and that the effect of gene *A* equals that of gene *B* in increasing height, each adding 2 inches to the height

What is the expected ratio as to height among the offspring of two dihybrids, *AaBb* × *AaBb*?

Construct a bar graph, or a histogram, showing the expected proportion of the offspring of each height Indicate by the height of the bars the frequencies of each class, beginning with the shortest on the left and proceeding to the tallest on the right

3. If a third gene (*C*) having the effect of increasing the stature 2 inches is added to genes *A* and *B* mentioned in Problem 2 (*AABBCC* = 6 feet 4 inches, *aabbcc* = 5 feet 4 inches), what is the expected ratio from a mating between trihybrids (*AaBbCc* × *AaBbCc*)?

Construct a bar graph showing the distribution of heights of offspring in the same manner as in Problem 2

Note In one experiment with sweet peas, Bateson and Punnett found that a dominant gene (*B*) converted the red pigment into purple A cross between two white plants gave all purple-flowered plants, as follows. *CCrrBB* (white) × *ccRRbb* (white) = *CcRrBb* (purple)

4 Show the expected result of a cross between two white sweet peas of the following constitution *CCrrBb* × *ccRRBb*

5. Show the expected result of a backcross of a purple sweet pea (*CcRrBb*) to a white (*ccrrbb*)

6. Show the ratio resulting from the self-fertilization of a trihybrid (*CcRrBb*).

Note Using the letters for the various color mutations in guinea pigs as listed on pages 91 and 92, show the visible ratios expected from the following crosses Assume that all animals are *SS*, hence free from white spotting

7. Brown, red spotted (*eeaaCcbbPp*) × pale brown, yellow spotted (*eeaaccbbpp*).
8. Black (*EEaaCCBbPP*) × pale sepia (*EEaaCCBbpp*)
9. Brown, red agouti (*EeAaCCbbPP*) × pale brown, yellow agouti (*EeAaccbbpp*)

10. What is the chance of obtaining a pale-brown guinea pig from the following cross Black, red agouti (*EeAaCcBbPp*) × pale sepia, yellow agouti, yellow-spotted (*eeAaccBbpp*)?

Note The ordinary domesticated guinea pig is smooth-haired, like the wild rodent (*Cavia cutleri*) of South America that is considered its ancestor The individual hairs slope backward on the body and downward toward the tips of the toes, as on most mammals There is a common variety of guinea pigs known as *rough*, which is the result of a dominant mutation (*R*) It was discovered by W. E Castle, Harvard geneticist, in 1905 The roughness is due to changes in the normal hair direction: there may be rosettes crests, partings, whorls, and hair reversals in a variety of patterns.

Another gene (*M*), discovered by Sewall Wright in 1916, reduces the roughness Gene *M* shows incomplete dominance All possible combinations of the genes *R* and *M* have been studied by Wright, and their effects determined as follows:

RRMM, *RrMM* } *Slight rough*, with hair reversals on the hind toes at least, sometimes on the front toes also, and occasionally with a crest along the back

RRMm, *RrMm* } *Modified rough*, usually a single pair of rosettes on the back or, less often, a crest on the back, reversals on the toes

RRmm, *Rrmm* } *Full rough*, usually two pairs of rosettes on the back, rosettes on the head, reversals on belly and toes

rrMM, *rrMm*, *rrmm* } *Smooth*, as in the wild cavies and the ordinary guinea pig Gene *M* is unable to express itself in the absence of *R* Wild cavies are *rrMM*

11. Calculate the expected phenotypic ratios from the following matings, designating the four visible classes with the italicized terms in the preceding paragraphs.

a. *rrMM* × *RRmm*
b. *RrMm* × *RrMm*.
c. *Rrmm* × *RrMm*.
d *rrMm* × *RrMm*.

12. In tomatoes two pairs of genes affect the color of the ripe fruit as follows *R*, red flesh; *r*, yellow flesh, *Y*, yellow skin, *y*, colorless skin Dominance is complete for red flesh and yellow skin the interactions of the genes give fruits of the following four colors· *R–Y–*, red, *R–yy*, pink, *rrY–*, yellow, *rryy*, cream Calculate the expected phenotypic ratios from the following crosses

a. Pink (*Rryy*) × yellow (*rrYy*)
b. Red (*RrYy*) × cream (*rryy*).
c. Red (*RrYY*) × pink (*Rryy*)
d Red (*RRYy*) × yellow (*rrYy*)
e Red (*RrYy*) × red (*RrYy*)

13. A pair of genes affects leaf shape in tomatoes as follows *C*, normal, deeply indented leaf (*cut*), *c*, shallow notches, resembling a potato leaf (*potato*) Calculate the expected ratios from the following crosses (see preceding problem for genes affecting color).

a Red, cut (*RRYyCc*) × cream, potato (*rryycc*)
b Pink, potato (*Rryycc*) × yellow, cut (*rrYyCc*)
c Red, potato (*RrYycc*) × cream, cut (*rryyCc*).
d Yellow, potato (*rrYycc*) × red, cut (*RrYYCc*)

14. In corn the dominant genes, *A*, *C*, and *R*, are all necessary for the production of red aleurone color. A plant that carries a double dose of any one of the three recessive alleles (*aa*, *cc*, or *rr*) produces white seeds only A fourth dominant gene, *I*, inhibits the production of aleurone pigment, regardless of any other genes that may be present A fifth dominant gene, *P*, converts any red pigment that is produced to purple *P*, however, has no effect when acting by itself

Show the expected phenotypic ratios from self-pollination of the following:

a. *AACCRrPpii*.
b. *AACcRrPPii*
c *AACCRrPPIi*.
d. *AACCRRPpIi*.

15. Calculate the expected phenotypic ratios from the following crosses in corn:

a *AaCcRrPPii* × *AaCcRrPPii*
b. *AaCcRrPpii* × *aaccrrppii*

16. Wright found that in the guinea pig the six coat-color genes *S*, *E*, *A*, *C*, *B*, and *P* are inherited independently of one another In the guinea pig there are 32 pairs of chromosomes. Calculate the probability that six genes chosen at random in the guinea pig will each be found on a different chromosome.

7

MULTIPLE ALLELES

The word *allele* is a general term used to denote the alternative forms of a gene or of the character governed by the gene Thus the gene for vestigial wing in Drosophila (Fig 6, page 18) and the alternative normal gene are alleles An older term, *allelomorph* (*allelon*, of one another; *morph*, form), is frequently employed, introduced by Bateson in the early days of Mendelism, its usage is now yielding to the shorter term allele.

The studies of linkage and crossing over, discussed in the next chapter, have shown that all the alleles of a given gene occupy the same locus on the chromosome Only a single allele, of course, is present at any one time at a given locus

For a good many years it has been known that more than two alternative forms of a gene may exist Three or more in a set make up what is known as a series of *multiple alleles* Multiple alleles have been discovered in many species of plants and animals

Several series of multiple alleles have been discovered in man Among these are the series responsible for the blood groups A-B-O, M-N-S-s, and Rh-Hr

The principles governing the relationships of the alleles in a series have been studied thoroughly in a number of plants, in Drosophila, and in mammals In Drosophila many series are known There are, for example, at least eight alleles of the vestigial gene, all affecting the size, shape, and structure of the wing, and 14 alleles of the white-eye gene, all affecting eye color, producing a series of eye colors ranging from white through cream and pink to red These two series illustrate the fact that the alleles in a series usually produce their major effects upon the same character or process in the organism and that the differences in their effects are quantitative.

In rodents several series of multiple alleles have been demonstrated According to Castle, at least five series are known in rabbits. One of these is a series of triple alleles responsible for blood groups similar to those in man,[1] in another (the albino series) six alleles have been identified. In the house mouse, at least four series are known.

[1] C E Keeler and W. E. Castle, Blood Group Inheritance in Rabbits, *J. Heredity*, 25:433–439, 1934

THE GUINEA PIG

In the guinea pig three series have been found, all affecting pigmentation. Since the multiple alleles in the guinea pig illustrate the principles common to other organisms, they will be described in some detail

The wild-type guinea pig (agouti pattern) was described on page 89 A mutant variety has red spots; in the absence of white spots the red hairs tend to be dispersed, giving the animal a brindled, or "tortoise shell," appearance The amount of red varies from only a few red hairs to large red areas A third allele eliminates all black from the hair, leaving the animal self red Pigmentation of the eyes is not affected by this series Summarizing the effects mentioned we have

E, No red spots
e^p, Tortoise shell (red spots)
e, Self red

As in the above example, superscripts are usually added to the symbols in order to differentiate the genes of a series of multiple alleles E is dominant over both of the other alleles, and e^p is dominant over e It is interesting to note that in rabbits a series apparently homologous with this one in guinea pigs contains at least four alleles

In multiple alleles one gene of the series usually is completely dominant over the others. Ordinarily this gene is the one prevalent in the wild species, and from it the others have arisen by mutation Dominance among the other members of the series is sometimes complete, more often it is incomplete. There is no way of representing, by means of symbols, the dominance situation of the lower alleles As a general rule the genes may be arranged in a series showing graded effects on a character, as in the above example.

A second series of triple alleles in guinea pigs, the *agouti series*, concerns the distribution of pigment in the individual hairs In the wild-type guinea pig the agouti band (page 90) is wider and lighter in color on the underparts of the animal than elsewhere, causing the belly to appear yellow. As already noted, a recessive allele of the gene A eliminates the band, converting the agouti pattern to black.

A third allele, a^r, is intermediate, both in effect and as to dominance, a^r reduces the width of the yellow band so that the agouti pattern is more or less uniform all over the body. The agouti gene A is dominant over the other two, and a^r is dominant over a In their effects, these alleles form a graded series in which the amount of red or yellow pigment in the individual hairs is reduced in two steps, thus:

A, Agouti, light-bellied
a^r, Agouti, uniform
a, Non-agouti (no banding of hairs)

The third series of multiple alleles found in guinea pigs is considerably more complex than the other two. Known as the *albino series*, it seems to be of general occurrence in mammals, although not identical among them. In guinea pigs five alleles make up the albino series. Assuming that the background of other genes is that found in the wild type, the effects of this series may be summarized briefly as follows:

TABLE 8. EFFECTS OF THE ALBINO SERIES OF GENES IN GUINEA PIGS IN ALL POSSIBLE COMBINATIONS*
(Numbers indicate relative intensities of pigment.)

Genes	Black (grade)		Yellow (grade)		Eye color
$C-$	Black	21.0	Red	10.6	Black
c^kc^k	Dark sepia	20.1	Yellow	7.1	Black
c^kc^d	Dark sepia	19.4	Yellow	7.2	Black
c^kc^r	Dark sepia	20.5	Yellow	4.6	Black
c^kc^a	Dark sepia	18.5	Yellow	4.6	Black
c^dc^d	Medium sepia	16.9	Yellow	7.0	Black
c^dc^r	Dark sepia	19.1	Cream	4.1	Black
c^dc^a	Light sepia	14.0	Cream	4.2	Black
c^rc^r	Dark sepia	20.1	White	0	Dark red
c^rc^a	Light sepia	15.5	White	0	Light red
c^ac^a	White	0	White	0	Pink

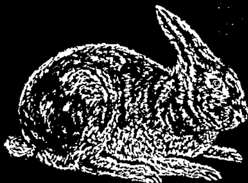
* After Wright.

C, "Intense": coat color black and red, eyes black
c^k, "Dark-dilution": coat color dark sepia and yellow, eyes black
c^d, "Light-dilution": coat color medium sepia and yellow, eyes black
c^r, "Red-eyed dilution": coat color dark sepia, yellow reduced to white, eyes dark red
c^a, Albinism: coat white, eyes pink

The effects of all of the possible combinations of these five alleles have been studied exhaustively by Wright.[1] His results are summarized in Table 8. The numbers in the columns headed black and yellow, re-

[1] Sewall Wright, The Factors of the Albino Series of Guinea Pigs and Their Effects on Black and Yellow Pigmentation, *Genetics*, 10:223–260, 1925; and The Effects in Combination of the Major Color-factors of the Guinea Pig, *Genetics*, 12:530–569, 1927.

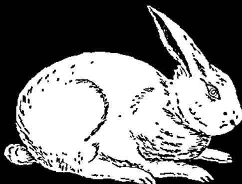
(1)



(2)



(3)



igure 35. Triple alleles in the rabbit (1) Wild type, intense color, CC. (2) Iimalayan, black-tipped white, pink eyes, c^hc^h. (3) Albino, white, pink eyes, c^a.

spectively, represent average intensities based upon a scale in which 21 0 is black, 10 6 is red, and 0 is white in each of the two color series

An inspection of Table 8 reveals a number of interesting facts We note first the complete dominance of C over the other four alleles and the incomplete dominance among the four lower members If the alleles are arranged in the order of their quantitative effect upon one process, as upon the formation of yellow pigment, they are not in similar order as to their effect upon black pigment Note for example that c^r produces almost as much black pigment in the hair as the intensity gene C, in striking contrast is the low ability of c^r to produce pigment in the eye and its total inability to produce yellow pigment.

A similar albino series is found in the rabbit, three alleles of which are shown in Fig 35 Wright's theory concerning the physiological effect of the albino series of alleles is summarized in the following quotation:

> It is suggested that the factors of the albino series determine the rate of some one process fundamental to all pigmentation and that the irregularities in the order of effect on different kinds of pigment, or in different regions of the body, are due to subsequent physiological processes with which the albino series of genes has nothing to do Among such processes one which determines a higher threshold for yellow than for black finds extensive corroboration in the albino series of other mammals. A tendency for the production of yellow to interfere with the production of black is suggested by the guinea pig series. The differences between intensity of black in the fur and the eye suggest that competition from yellow is lacking in the eye, which thus shows more simply than the fur the effects of the different genes on intensity of black.

As we shall see in a later chapter, the genetic analysis of hair color in man still offers considerable difficulties. It is probable that some of these difficulties are due to the fact that in man one or more series of multiple alleles exist, just as they do in guinea pigs and other mammals. The solution of the problem in human beings must wait on the collection of more extensive pedigrees than those now available. There is no reason for thinking that the principle of multiple alleles has any peculiar relationship to hair color in mammals, the principle seems to apply widely to genes affecting all sorts of characters in plants and animals We have chosen hair color in the guinea pig merely because this is one of the best-worked-out cases The best-known cases of multiple allelism in man are those affecting the many serological differences in human blood, giving numerous series of blood groups and blood types Two of these series will now be described

O-A-B BLOOD GROUPS

In recent years blood transfusions have come to be widely used following severe hemorrhages and as a treatment in various diseases The

knowledge that the blood donor and the recipient must be tested for compatibility before a transfusion can be done safely has made us all conscious of the existence of individual differences in human blood. Many, however, do not realize that these differences are hereditary

There are four major blood groups, O, A, B, and AB Classification of an individual is carried out by means of a simple laboratory test using a drop of blood and testing sera The basis of the test is the property of the serum of an individual of one group to cause a clumping (agglutination) of the corpuscles of an individual of another group, according to a definite system, to be described presently

The fact that such differences exist was not discovered until 1900, when Dr. Karl Landsteiner, an Austrian physician, curious to see whether any reaction occurred when bloods of human individuals were mixed, such as was known to take place in the mixing of bloods of different species, tried the experiment of mixing the serum of one person with the blood of another. He found that in certain cases a marked agglutination reaction followed, while in other cases there was no reaction On the basis of his studies Landsteiner recognized three distinct human blood groups The fourth group was discovered in 1902 by two of his students

Subsequently Landsteiner came to this country where he continued his researches on blood at the Rockefeller Institute for Medical Research For his many original contributions he was awarded the Nobel prize in medicine for 1930.

Beginning sometime in the early nineteenth century, blood transfusions had been made from person to person, frequently with fatal results The fatalities, it now seems probable, followed the mixing of incompatible bloods, resulting in the clumping and/or hemolysis of the donor's corpuscles in the blood vessels of the recipient In blood transfusions the serum of the donor is not likely to produce a severe reaction, even though it is antagonistic to the corpuscles of the recipient, because of the dilution with the recipient's own serum The chief danger comes from introducing corpuscles which are agglutinated or hemolyzed by the recipient's serum Surprising as it may seem, there is a possibility that a mother's blood may be of a type that will kill her own child if a transfusion is made from mother to child, while the blood of a member of a different race may be perfectly safe Since 1900 a vast amount of research on the blood groups of man has been done, including numerous studies of the mode of inheritance and racial significance of the groups

As to mode of inheritance, the existence of a series of three alternative genes (triple alleles) was demonstrated by a German investigator, F. Bernstein, in 1924. Every person has a pair—and only one pair—of these genes, which may consist of any one of the six possible combina-

spectively, represent average intensities based upon a scale in which 21.0 is black, 10.6 is red, and 0 is white in each of the two color series

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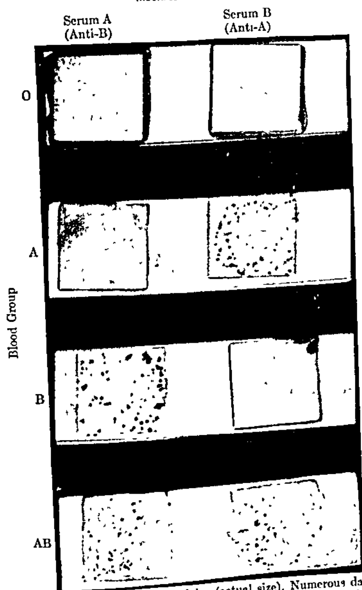


Figure 36 Blood grouping on glass slides (actual size). Numerous dark specks of various sizes indicate agglutinated red blood corpuscles. On slides that remain clear there is no agglutination (*From Wiener, "Blood Groups and Transfusion," 3d ed, Charles C Thomas*)

glutinogens The homozygous recessive individual (*ii*) produces neither agglutinogen. The general rule is that the plasma of an individual causes an agglutination of corpuscles containing agglutinogens not found in his own blood, in other words, each person produces agglutinins against agglutinogens which he does not possess

For a number of years the foregoing account was accepted as an adequate serological and genetic explanation of the observed facts. Further studies, however, have demonstrated that agglutinogen A may exist in either of two forms These have been designated as A_1 and A_2 This discovery means that there are two kinds of group A blood, depending on whether the agglutinogen is A_1 or A_2. Consequently there are two kinds of group AB individuals, A_1B and A_2B. According to Wiener,[1] approximately one-fourth to one-fifth of all group A individuals of European ancestry belong to subgroup A_2, the rest belong to subgroup A_1 A still higher frequency of A_2 is found among the Bantu natives of Africa A_2 is practically absent among the Mongoloids, Polynesians, and Australian Aborigines.

Serum from group B ordinarily contains agglutinins against both subgroups A_1 and A_2, so that in testing, the A_1's and A_2's are lumped together.

The mode of inheritance of the subgroups of groups A and AB now seems well established Beginning with the first studies, reported in 1927, numerous investigators in this country and abroad have, according to a tabulation by Wiener, examined a total of 1,068 families, with 3,134 children. These families include 16 different matings—all possible ones involving A_1 and A_2, in fact, except the rare combinations $A_1B \times A_2B$ and $A_2B \times A_2B$ The conclusion reached is that instead of a series of only three blood-group alleles I^A, I^B, and i, there exist four allelic genes, I^{A_1}, I^{A_2}, I^B, and i. The first three in the series are dominant over i, and I^{A_1} is dominant over I^{A_2}. The existing six phenotypes and their 10 genotypes are therefore as follows:

Phenotype	*Genotype*
O	ii
A_1	$I^{A_1}I^{A_1}$, $I^{A_1}i$, $I^{A_1}I^{A_2}$
A_2	$I^{A_2}I^{A_2}$, $I^{A_2}i$
B	I^BI^B, I^Bi
A_1B	$I^{A_1}I^B$
A_2B	$I^{A_2}I^B$

The frequency of the four groups (combining the subgroups of A and of AB) has been studied in practically every racial and national group in the world through the efforts of many investigators. A summary of the

[1] Alexander S Wiener, "Blood Groups and Transfusion," 3d ed, Charles C Thomas, Publisher, Springfield, Ill, 1943. This is an excellently written and illustrated book dealing with all aspects of the blood groups, including historical, clinical, genetic, anthropological, and medicolegal aspects

data is given by Wiener. From the anthropological point of view the results are most interesting All four groups are found to be present and widely distributed in all three major divisions of mankind—Caucasoids, Mongoloids, and Negroids—as well as in most of the racial subdivisions In the United States tests of many thousands of persons indicate the frequency of the groups to be roughly as follows O 45 per cent, A 41 per cent, B 10 per cent, AB 4 per cent These proportions are fairly typical of the peoples of western Europe As one travels eastward through Europe and Asia and southward into Africa and India, there appears a more or less gradual rise in the percentage of group B In Europe and Japan this rise is largely at the expense of group O, among African Negroes it is at the expense of group A; and on the continent of Asia it is at the expense of A or both O and A. There are high spots in the frequency of B in the centers of Asia and Africa, with a falling off in all directions

Among North American Negroes the group frequencies resemble closely those of the natives of West Africa, as might have been expected from the known origin of the Negroes in this country The figures for Negroes are approximately as follows O 47 per cent, A 28 per cent, B 20 per cent, AB 5 per cent.

In blood-group frequencies other African peoples may differ sharply from those of West Africa, as illustrated by the Pygmies of the Ituri Forest and the Bushmen of the Kalahari Desert

	No examined	O, %	A, %	B, %	AB, %
Pygmies*	1,032	30 6	30 3	29 1	10 0
Bushmen†	548	57 1	29 5	6 8	6 6
Bushmen‡	446	56 0	33 9	8 5	1 6

* William C Boyd, "Genetics and the Races of Man," Little, Brown & Company, Boston, 1950

† A. Pijper, Pygmies, Bushmen, and the Meaning of Travel, *Sci Monthly*, 70.409, 1950

‡ A Zoutendyk, A C Kopec, and A E Mourant, The Blood Groups of the Bushmen, *Am. J Phys Anthropol*, 11·361–368, 1953

The most striking variations from the distributions in the larger populations are found among certain small and isolated populations, as illustrated in the following:

	Number	O, %	A, %	B, %	AB, %
Australian Aborigines ..	398	33 9	66 1	0	0
Tuamotus (Polynesians)	176	48 3	51 7	0	0
Indians, pure (Peru)	200	100	0	0	0
Bush Negroes (Dutch Guiana)	336	83	0	17	0

With small populations like those in the above table we see that it is possible to have one or more alleles missing entirely.

Several attempts have been made to find some correlation between the blood groups and various other characters, including susceptibility to specific infections and other diseases. Suggestions of positive correlations between certain blood groups and susceptibility to specific diseases have been reported. There is no critical evidence that any of the groups has any selective advantage over any of the others. They may be merely illustrations of nonadaptive differences that have arisen through mutation and chance preservation under conditions of partial isolation resulting from barriers of one kind or another.

M-N-S-s BLOOD TYPES

In 1927 two additional hereditary agglutinogens, designated M and N, were discovered by Landsteiner and Levine in human blood. All persons so far tested have either one or the other or both of these and are therefore classified as type M, N, or MN. The frequencies of the three types are the same in persons of all four blood groups in a given population, indicating that the agglutinogens M and N have no relation to agglutinogens A and B.

Human beings do not as a rule produce agglutinins against the agglutinogens M and N, in contrast to their normal production of agglutinins against the agglutinogens A and B. Anti-M rarely occurs in human serum, anti-N even more rarely, either spontaneously or as a result of blood transfusion.

The test sera containing the agglutinins or antibodies against the agglutinogens M and N are obtained from rabbits injected with human blood of types M and N, respectively.

The mode of inheritance of the M-N types was correctly deduced by Landsteiner and Levine. Wiener summarizes the results of investigations by the original discoverers and by numerous later workers; 2,165 families with 6,718 children are included in his table. The results demonstrate the presence of two alleles, L^M and L^N (using the first letter of the names of the discoverers as the basic gene symbol): type M is always of genotype L^ML^M, type N is L^NL^N, and type MN is L^ML^N. Each gene produces its characteristic agglutinogen when present in single dose, as well as in double dose. This is a general rule with other agglutinogens that have since been discovered in human blood.

In 1947 two investigators in Australia[1] found a new agglutinin in human blood that has the effect of subdividing each of the three M-N types

[1] R. J. Walsh and Carmel Montgomery, A New Human Isoagglutinin Subdividing the MN Blood Groups, *Nature*, 160:501, 1947.

into two subtypes. This agglutinin was called anti-S, and the corresponding agglutinogen, S. The red blood cells of individuals of types M, N, and MN react either positively to anti-S serum (type S) or show no reaction to anti-S serum (type s) In 1951, American investigators[1] found in human blood an agglutinin (anti-s) which agglutinates the cells in persons of type s, whose corpuscles therefore carry the corresponding agglutinogen, s.

According to one genetic theory, there are four alleles in the M-N series; these may be designated as L^{MS}, L^{NS}, L^{Ms}, and L^{Ns} The superscripts indicate the agglutinogens produced by each of the four alleles. With four alleles there are ten possible genotypes, and in this case nine phenotypes, as follows:

Phenotypes	*Genotypes*
M S	$L^{MS}L^{MS}$
M Ss	$L^{MS}L^{Ms}$
M s	$L^{Ms}L^{Ms}$
MN S	$L^{MS}L^{NS}$
MN Ss	$L^{MS}L^{Ns}$, $L^{Ms}L^{NS}$
MN s	$L^{Ms}L^{Ns}$
N S	$L^{NS}L^{NS}$
N Ss	$L^{NS}L^{Ns}$
N s	$L^{Ns}L^{Ns}$

Tests for the M-N-S-s types may be made with the slide technique as described for the A-B-O groups So far, agglutinins anti-S and anti-s have been found in the blood of only a few persons But everyone has in his red corpuscles agglutinogen S, or s, or both S and s Consequently all persons may be classified into the nine phenotypes The M-N-S-s series has great value in questions of disputed parentage and in anthropology. Sanger and Race[2] consider that it is potentially the most useful of all blood-group systems in the solution of problems of identity and parentage. Wiener[3] has presented calculations showing the possible usefulness of the M-N-S-s types in questions of disputed identity, disputed paternity and maternity, interchange of infants, and zygosity of twins

Race and Sanger[4] give methods of calculating the relative frequencies of the four alleles in a population and cite the following frequencies for three populations that have been tested

[1] P Levine, A. B. Kuhmichel, M Wigod, and E Koch, A New Blood Factor, *s*, Allelic to *S*, *Proc Soc Expt Biol Med*, 78:218–221, 1951

[2] Ruth Sanger and R R Race, The MNSs Blood Group System, *Am J Human Genet*, 3:332–343, 1951

[3] A. S Wiener, Heredity of the M-N-S Blood Types: Theoretico-statistical Considerations, *Am J. Human Genet*, 4:37–53, 1952

[4] R R Race and Ruth Sanger, "Blood Groups in Man," Charles C Thomas, Springfield, Ill, 1950.

Alleles	L^{MS}	L^{Ms}	L^{NS}	L^{Ns}
English	0.25	0.28	0.08	0.39
Australian Aborigines	0.00	0.26	0.00	0.74
New Guinea natives	0.05	0.15	0.08	0.72

The Australian Aborigines and the natives of New Guinea are evidently similar in their frequencies of the agglutinogens M and N, but differ strikingly from one another in agglutinogen S, which is entirely lacking in the Australian Aborigines. The English differ from both of these groups in the frequencies of M and S.

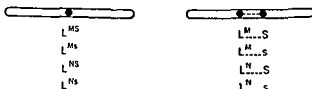


Figure 37. Diagrams of chromosomes, to show that a single gene with a double effect (*left*) is transmitted in the same manner as two completely linked genes with separate effects (*right*). On the left are four alleles of a single gene, on the right, four combinations of two completely linked genes, each gene with two alleles.

Although the genetic evidence from the study of families supports the theory of a series of four alleles, as set out above, the technical question still remains as to whether the agglutinogens S and s may not be produced by a second pair of alleles situated close to the locus of *M/N*—so close in fact that the two genes are permanently linked. It is evident from an inspection of the diagram in Fig. 37 that two completely linked genes would be transmitted in the same manner as if they constituted one gene with a double effect. For practical purposes in the solution of problems we will therefore consider this series as one, with four alleles, each allele having a double effect.

PROBLEMS

Note: In the first four problems calculate the expected phenotypic ratios from the various matings in guinea pigs, using page 91 and Table 8 for reference. Assume in every case that the animals are homozygous for the genes for red spotting and non-agouti.

1. Mating of two light-sepia, cream, black-eyed animals ($c^dc^a \times c^dc^a$)
2. Cross of a dark-sepia, white, dark-red-eyed animal with a light-sepia, white, light-red-eyed animal ($c^rc^r \times c^rc^a$).
3. Mating of two light-sepia, white, light-red-eyed animals ($c^rc^a \times c^rc^a$).

4. Cross between black-eyed and pink-eyed $(Pp\,c^rc^a) \times (pp\,c^rc^a)$

5. Calculate the expected phenotypic ratios among the children of persons of the following blood groups:

a $O \times A(I^Ai)$.
b $O \times AB$.
c $A(I^Ai) \times A(I^Ai)$.
d $A(I^Ai) \times B(I^BI^B)$.
e. $A(I^Ai) \times B(I^Bi)$.
f. $A(I^AI^A) \times AB$.
g $B(I^Bi) \times AB$

6. Are there any cases in which it is possible, knowing the blood group of a child, to state positively the blood group of its parents? Explain

7. If matings are at random with respect to the blood types, what percentage of marriages among Caucasoids in the United States should be M × M, M × MN?

8 In a case of disputed parentage the baby was of blood type N and the mother was of type MN. State all that you can about the type of the father

9 In a case of disputed parentage two babies were of types MN and N, respectively Their mothers were also of types MN and N, but it was uncertain to which mother either baby belonged The husband of woman MN was of type N, the husband of woman N was of type M To which mother did type N baby belong?

10. A child whose father was of doubtful identity was found to be of blood type Ns Its mother was of type MNs What types are possible in the father?

11. List all the possible *genotypic* matings among the MN blood types, ignoring the Ss agglutinogens

12. How many different *genotypic* matings are possible, including the Ss agglutinogens? (Show your method of calculation.)

13. According to one theory of the nature of alleles, known as the *presence and absence hypothesis*, proposed by Bateson and Punnett, a recessive character is due to the absence of a dominant gene Morgan suggested that the occurrence of multiple alleles made this hypothesis untenable Why does this conclusion logically follow?

8

LINKAGE AND CROSSING OVER

As we have seen, the principles of segregation and independent assortment can account for the appearance of many new traits and combinations of traits in living things Since the genes are carried in the chromosomes it is obvious that the larger the number of chromosomes the greater will be the number of possible combinations of genes and traits resulting from independent assortment.

If we could imagine each gene as occupying its own special chromosome, we would then have independent assortment among all the genes But such an idea is contrary to the facts In organisms that have been studied intensively, such as corn (*Zea mays*) and the fly *Drosophila melanogaster*, hundreds of Mendelian traits have been found. Corn has ten pairs of chromosomes and Drosophila has only four pairs We conclude that many genes must occupy a single chromosome This logical conclusion is supported by various lines of evidence and may now be regarded as a fact

The tendency of genes to be passed on to the next generation in groups is known as *linkage*. Linkage has been found to apply generally in plants and animals If we ignore for the moment the effect of multiple alleles in producing variability among organisms, we might conclude that linkage is a severe restriction upon the possible variability among organisms For example, in *Drosophila melanogaster*, with its four pairs of chromosomes, only 16 different combinations of maternal and paternal chromosomes are possible in the gametes At fertilization, from 16 kinds of gametes, the possible kinds of genotypes among the zygotes number 81. This is a very small number compared to the number of combinations possible if each gene known in Drosophila were independent of all the others

The limitations inherent in the linkage system are, however, largely compensated for by still another mechanism for increasing variability This mechanism is known as *crossing over*. Crossing over may be defined as *the mutual exchange of blocks of homologous genes located on the two members of a pair of chromosomes*. As a result of crossing over, most of the combinations theoretically possible among the genes eventually occur.

The first observations leading to the discovery of linkage and crossing over were made in England by Bateson and Punnett in experiments on sweet peas. For the fullest development of the principle of linkage and crossing over, however, we have to thank the American biologists T. H. Morgan and his students and associates, especially A. H. Sturtevant,



Figure 38. Thomas Hunt Morgan, 1866–1945 (Taken 1932.)

H. J. Muller, and C. B. Bridges. The epoch-making experiments upon which our present conception of linkage and crossing over is based were begun by Morgan about 1910, at Columbia University. The fruit fly Drosophila, which has come to occupy a prominent place in research on the structure and behavior of chromosomes, was used in the experiments. For his contributions in this field Morgan received many honors, including the Nobel prize in medicine for 1933. In order to illustrate linkage and crossing over we may well select a case in Drosophila worked out by Morgan.

LINKAGE AND CROSSING OVER IN DROSOPHILA

Two recessive mutations discovered by Morgan about 1920 are shown in Fig. 39. One of these, known as *black*, is much darker than the normal gray-bodied fly. The other, *vestigial*, has wings which are reduced to useless stubs. In both cases, if crossed with normal flies, these mutants give the typical 3 : 1 ratio in the third (F_2) generation. From a cross between a pure long-winged black fly and a pure gray-bodied vestigial fly (Fig. 39) the offspring are all normal, since each parent gives to the offspring the normal gene lacking in the other. When one of the normal dihybrid females from this cross is backcrossed with the double recessive (black vestigial) the resulting ratio is very different from the 1:1:1:1 ratio we have learned to expect in a backcross mating of a dihybrid to a double recessive. The actual results of such an experiment are shown in Fig. 39.

We note that the ratio is symmetrical in that the two combinations of traits present in the grandparents are equally numerous, as are also the two new combinations. The original combinations, however, make up 83 per cent of the total number, instead of 50 per cent, as would be the case for independent assortment. The rest of the offspring, amounting to 17 per cent, are new combinations. The new combinations are known as *recombinations*, or *crossovers*. As we shall see later, it was purely accidental that two mutants were chosen that showed 17 per cent crossing over. The percentage of crossing over has direct relationship to the distance the genes lie apart on the chromosome, and two other genes chosen at random would probably show a different percentage.

Morgan showed that this unusual ratio fits perfectly into the theory that the genes black and vestigial are on the same chromosome; in other words, that they are linked, and that the dihybrid produces four types of gametes in the same ratio as that of the character combinations in its offspring, namely, in this case:

(*Bv*)	(*bV*)	(*bv*)	(*BV*)
41.5%	41.5%	8.5%	8.5%

(Symbols of genes located on a single chromosome are customarily enclosed in parentheses.)

The double-recessive parent produces only one kind of gamete (*bv*). Since both genes in this gamete are recessive, they do not affect the ratio: the characteristics of the offspring in a backcross to the double recessive correspond in every case to the gene make-up of the gametes of the dihybrid.

The dihybrid female parent obviously received from its parents the two chromosomes (*Bv*) and (*bV*). The only way in which the gametes (*bv*) and (*BV*) could be produced by this female was through an exchange of

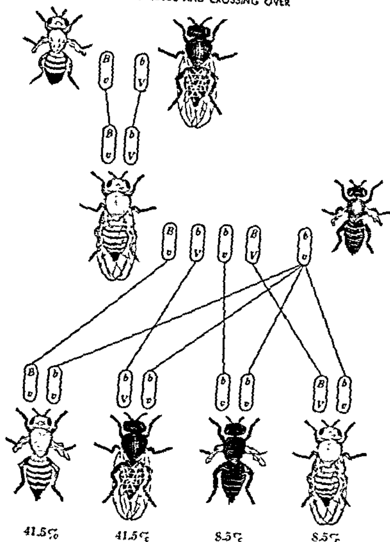


Figure 39. Crossing over in *Drosophila*. A gray vestigial-winged male is crossed with a black long-winged female. One of the female off-spring is backcrossed with a black vestigial male; the result is four types of off-spring in the proportions indicated. (*From Morgan, "The Physical Basis of Heredity," J. B. Lippincott Company, 1919.*)

genes between the parental chromosomes. This exchange, or crossing over, gave rise to the two new combinations of traits in the offspring. It is highly significant that in all such experiments both recombinations, as well as both parental combinations, occur with equal frequency.

If the above experiment is modified by using in the backcross mating,

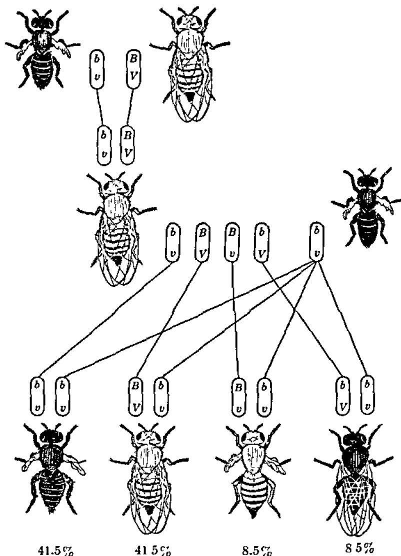


Figure 40. Crossing over in Drosophila. A black vestigial-winged male is crossed with a gray long-winged female. One of the female offspring is backcrossed with a black vestigial male; the result is four types of offspring as indicated Note that the combinations of traits shown by the crossovers are the same as those of the noncrossovers in Fig 39. (*From Morgan, "The Physical Basis of Heredity," J B Lippincott Company*, 1919.)

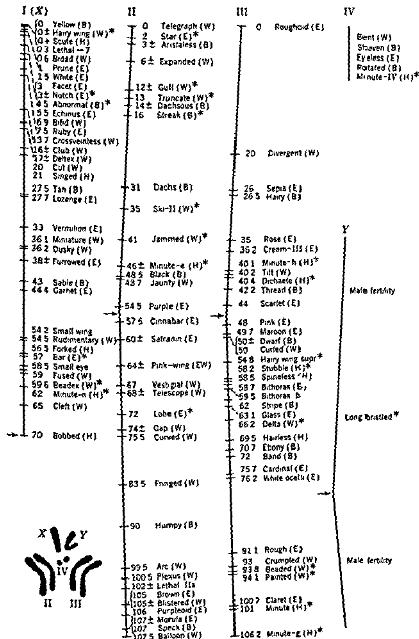


Figure 41. Linkage map for *Drosophila melanogaster*, showing serial order of the genes of many of the most frequently used mutants. Letters in parentheses indicate parts of the fly involved: (*B*) body; (*E*) eye; (*H*) hairs, (*W*) wings. Arrows indicate positions of centromeres; asterisks indicate dominant traits (*From Sharp, "Fundamentals of Cytology," McGraw-Hill Book Company, Inc., after Morgan, Sturtevant, and Bridges, and C. Stern.*)

a female obtained from a cross between wild type and the double recessive and which, therefore, has both dominant genes on one chromosome and both recessive genes on the other (Fig. 40), the same percentage of recombinations among the offspring is obtained as in the previous experiment The combinations of traits in the crossovers and the noncrossovers are, however, reversed in the two experiments, as can be seen by comparing Figs 39 and 40. In the one experiment the traits shown by the crossovers are the same as those shown by the noncrossovers in the other, and vice versa.

These experiments prove that the normal alternatives of the genes for black and for vestigial cross over with the same frequency as do the black and the vestigial genes themselves—a result that agrees with the hypothesis that such alternatives, or *alleles*, as they are known, occupy corresponding positions, or *loci*, on the chromosomes. Expressed otherwise, it is the position of the genes rather than their nature that determines the percentage of crossing over

Several hundred genes in Drosophila have been tested, one with another, in order to discover their linkage relationships. All have been found linked with other genes, not one being inherited independently of all others The genes tested fall into four linkage groups, in which every gene shows linkage with all other genes of the same group, but shows independent assortment with all genes of the other three groups The number of linkage groups corresponds exactly with the number of pairs of chromosomes Furthermore, there is a correspondence between the number of genes in each of the four linkage groups and the relative lengths of the four chromosomes, respectively Thus all but about a dozen of the known genes belong to the three groups representing the three longest chromosomes, the rest are located on the tiny fourth chromosome These facts are all set forth in the linkage map for Drosophila (Fig 41).

Experiments show that the percentage of crossing over between any two given genes is constant provided a uniform genetic stock and standardized environment are used, so that if the experiment is repeated under the same conditions the results may be predicted.

EXPLANATION OF LINKAGE AND CROSSING OVER IN CORN

The principle of linkage and crossing over established in experiments with Drosophila applies also to other organisms. In most species, however, crossing over occurs in both sexes, rather than in females only, as in Drosophila. In hermaphroditic plants such as Indian corn (maize) it takes place in both the male and the female parts of the plant, and as in Drosophila, the number of linkage groups agrees with the number of chromosome pairs

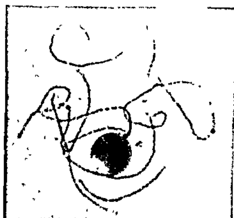


Figure 42. Photomicrograph of the 10 chromosomes of maize at pachynema during late prophase. Each apparently single chromosome at this stage consists of a synapsed pair. The large nucleolus will disappear at the end of prophase. (*From Morgan, Jr., J. Heredity.*)

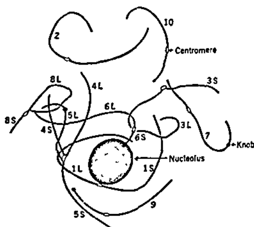


Figure 43. Diagrams of pachytene chromosomes of maize shown in Fig. 42 Each synapsed (bivalent) chromosome is drawn as a single line. Each of the 10 chromosomes is visibly distinguishable (*From Rhoades, J. Heredity*, **41**:60, 1950)

Corn is one of the most thoroughly analyzed of the plants, with more than 500 genes now known; and these all fall into 10 linkage groups corresponding to the 10 pairs of chromosomes in corn About 100 of the genes have been assigned to a specific locus on a particular chromosome (Chap 18) All 10 chromosomes, incidentally, are visibly distinguishable under the microscope (Figs 42 and 43). A similar stage is shown in Fig 44 Some of the chromosomes can here be identified by comparison with Fig 42 An American cytogeneticist, Dr. Barbara McClintock, is given chief credit for the identification of the individual chromosomes in corn

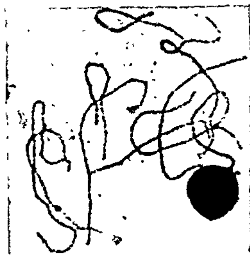


Figure 44. Photomicrograph of the 10 chromosomes of maize at pachynema during late prophase. How many of the chromosomes in this figure can you identify by comparison with Figs. 42 and 43? *(Courtesy of D T Morgan, Jr)*

and for the matching up of each chromosome with a particular linkage group Since the relation between the chromosomes and linkage is so well worked out in corn, we shall use this species in the following explanation of crossing over.

In corn a dominant gene known as *tassel seed* (*T*) has been located on chromosome 4. Tassel-seeded plants bear pistils as well as stamens in their tassels On this same chromosome there is a recessive gene responsible for *small pollen*, for which we will use the symbol *s*. These two genes show 10 per cent crossing over

Let us start with a plant that is heterozygous for tassel seed and small pollen, with one chromosome of the pair carrying both dominant genes and the other both recessives, as shown in Fig. 45. Using the diagram,

let us now follow the history of this pair of chromosomes during meiosis, our aim will be to observe the distribution of the genes to the four haploid cells that result from meiosis

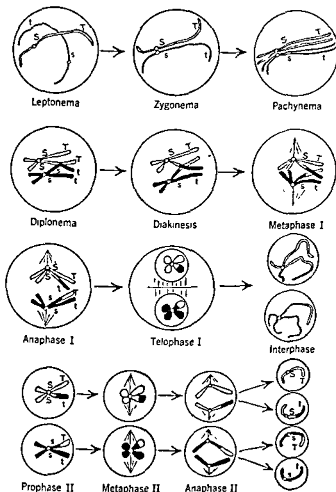


Figure 45. Diagram of meiosis showing one pair of chromosomes and a single chromatid exchange, resulting in four cells with two recombinations among the genes (*Modified after Rhoades.*)

In the early prophase of the first meiotic division, while the chromosomes are long and slender (leptonema), numerous granules, or chromomeres, differing in size and shape are arranged along the chromosome The chromomeres possibly represent the genes. The chromosomes making up the pair attract one another and come together side by side, with

similar chromomeres precisely matched up. This exact pairing of chromomeres and genes makes possible crossing over, which follows

The chromosomes now undergo a process of shortening, until finally they measure only a fraction of their former length (pachynema). Presently each chromosome appears as a double thread held together by a single centromere Each chromosome has duplicated its chain of genes

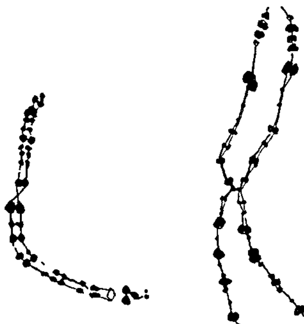


Figure 46. Drawings of prophase chromosomes in two species of plants *Left· Lilium pardalinum Right· Fritillaria lanceolata.* Note the identity in size and linear order of the particles (chromomeres) of the pairing chromosomes, and on the right the identity of the four strands (chromatids) One chiasma is shown in each figure. (*From Crane and Lawrence, "The Genetics of Garden Plants," 4th ed., The Macmillan Company; after Belling,* 1931.)

and now *consists of a pair of chromatids. The chromatids* continue to shorten as a result of coiling

As shown in Figs. 42 and 43, during pachynema all the 10 chromosomes can be identified by their relative lengths, their chromomere patterns, centromere positions, and the deeply staining knobs The chromosomes in corn are numbered from one to ten according to their relative lengths

In the next stage, known as diplonema, the centromeres move apart

and their chromatids follow in groups of two, forming loops and nodes A node is known as a chiasma (*chiasto*, X-shaped crossing), it is believed to mark a point of breakage of two homologous chromatids and their exchange of homologous sections Note that this exchange, *or crossing over*, brings the genes that lie on opposite sides of a chiasma into new combinations, as shown in the succeeding stages of meiosis in Fig. 45. Only two of the chromatids are shown undergoing crossing over at a given locus; this limitation is a general rule, which helps to account for the observed fact that not over 50 per cent of the offspring show recombinations due to crossing over.

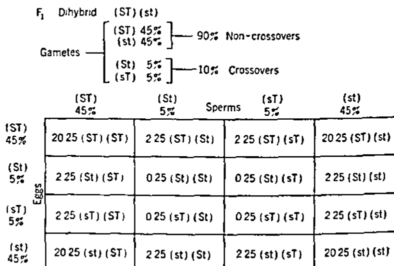
As the two centromeres move apart in the first meiotic division (Anaphase I), each accompanied by its two chromatids, we see that one of the chromatids carries a new combination of genes, while the other is unchanged During the second meiotic division the centromere divides, and each daughter centromere, with a single chromatid, moves away from its duplicate (Anaphase II). We now drop the term *chromatid* and refer to these objects as *chromosomes*. Note that in Anaphase II we have four different combinations of the two pairs of genes, two crossovers and two noncrossovers The breeding results, as well as chromosome studies, prove the correctness of the explanation represented in Fig 45

Summarizing, breeding experiments indicate that crossing over always involves the exchange of segments of chromatids rather than single genes Either chromatid of one chromosome may exchange segments with either chromatid of the homologous chromosome, irrespective, or largely so, of which strands have crossed over at other points A crossover can be detected only in case the chromatids entering into the trade differ from one another in at least two genes, because it is only such crossovers that result in visible recombinations among the offspring.

We shall now illustrate with the two genes of corn mentioned above the method of calculating F_2 ratios in a species where crossover gametes are produced in sperms as well as in eggs.

If a corn plant with small pollen (*s*) and normal flowers (*t*) is crossed with one that is homozygous for large pollen (*S*) and tassel seed (*T*), the hybrid will be tassel-seeded with large pollen, (*S T*)(*s t*) Self-fertilization of the hybrid will give the results shown in the checkerboard, Fig. 47.

It is evident that the only difference between the solution of problems in linkage such as this one and problems in independent assortment is that with linked genes the gametes are not formed in equal numbers: the sum of the crossover gametes does not exceed 50 per cent and may be any percentage whatever up to 50. *The resulting phenotypic ratios, therefore, are always expressed in percentages rather than in common fractions as in independent assortment.*



	(ST) 45%	(St) 5%	(sT) 5%	(st) 45%
(ST) 45%	20 25 (ST) (ST)	2 25 (ST) (St)	2 25 (ST) (sT)	20 25 (ST) (st)
(St) 5%	2 25 (St) (ST)	0 25 (St) (St)	0 25 (St) (sT)	2 25 (St) (st)
(sT) 5%	2 25 (sT) (ST)	0 25 (sT) (St)	0 25 (sT) (sT)	2 25 (sT) (st)
(st) 45%	20 25 (st) (ST)	2 25 (st) (St)	2 25 (st) (sT)	20 25 (st) (st)

Figure 47. Diagram showing the checkerboard method of calculating F_2 ratios with two linked genes in an organism having crossovers among both male and female gametes.

Summing up the phenotypes displayed in Fig. 47 we obtain:

70 25 per cent large pollen, tassel seed
4 75 per cent small pollen, tassel seed
4 75 per cent large pollen, normal seed
20 25 per cent small pollen, normal seed

LINKAGE IN MAMMALS

Linkage has been demonstrated in a number of mammals At least six linkage groups have been found in rabbits, in which there are 22 pairs of chromosomes In the mouse there are at least 13 known linkage groups, with 20 pairs of chromosomes (see Chap. 19). In guinea pigs only one case of linkage has been reported, in spite of intensive tests of a fair number of genes The failure to find others is probably related to the large number of chromosomes (32 pairs) in the guinea pig.

In man relatively little progress has been made in the study of linkage, except in the case of sex linkage, considered in a later chapter The comparatively large number of human chromosomes (24 pairs) and the small size of human families are two of the factors that make the detection of linkage difficult in man. Special statistical methods have been developed for this purpose, and several cases of linkage have been reported. We may safely predict that in due time many human genes will be located on chromosome maps Such a development would have great theoretical interest as well as practical importance. A knowledge of the

linkage relationships of human genes would permit more accurate predictions of the characters in the offspring of a given mating than is now possible. For example, let us suppose that there is a highly undesirable dominant gene (D) on the same chromosome as the one that carries the gene for the O-A-B blood groups. Also suppose that these genes have been found to show 1 per cent crossing over. Gene D expresses itself at about age 40 In a pedigree such as the one below we could, by testing the blood of the children, predict with 99 per cent accuracy whether the child carried gene D or not.

Parents O $(i\ d)(i\ d) \times (I^A\ D)(I^B\ d)$ AB

Gametes $(i\ d)$ ↓ ; ↓ $(I^A\ D)$, $(I^B\ d)$ noncrossovers (99%); $(I^A\ d)$, $(I^B\ D)$ crossovers (1%)

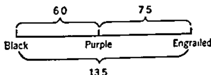
Children $(i\ d)(I^A\ D)$, $(i\ d)(I^B\ d)$ noncrossovers (99%); $(i\ d)(I^A\ d)$, $(i\ d)(I^B\ D)$ crossovers (1%)

Of group A children 99 per cent would be expected to develop the trait, while only 1 per cent of those of group B should develop it

MAPPING CHROMOSOMES

Crossing over between linked genes may be as little as 1/10 of 1 per cent, on up to 50 per cent, depending on the two genes that are chosen On the basis of their mutual crossover frequencies the genes in a chromosome may be arranged in a definite order along a single line (Fig 41). This is, in fact, the only satisfactory way of representing graphically their relationships

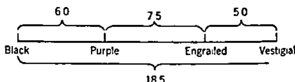
To illustrate the principle by an example let us consider two linked recessive genes in Drosophila, black (a body color) and purple (an eye color), both on chromosome II. The crossover frequency of these two genes is 6.0 per cent. A third gene, engrailed (a body character), lies on the same chromosome as the other two Its crossover frequency with purple is 7.5 per cent. Black and engrailed cross over with a frequency of 13 5 per cent, which is the sum of the other two These three genes may therefore be arranged on a graph, commonly known as a *chromosome map*, as follows.



In fact, no other sequence of these three genes in a straight line will fit the experimental results

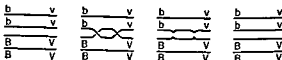
Genes are placed on the map in the linear order determined by their crossover relationships. The locus of each is indicated by a number. The difference between the numbers of two neighboring genes gives the percentage of crossing over that has been found between the two genes

Suppose that we now wish to locate the vestigial gene on the map. As we have seen, Morgan found that vestigial and black cross over to produce 17 per cent recombinations Does the vestigial gene lie to the right of black, i e., beyond engrailed, or does it lie to the left of black? To answer this question, vestigial and engrailed flies are mated and the dihybrid is backcrossed as in Morgan's experiment with vestigial and black. The results show 5 per cent crossing over between vestigial and engrailed Vestigial therefore must be placed to the right of engrailed as follows.



If vestigial were placed to the left of engrailed it is obvious that it would not give 17 per cent crossing over with black By a continuation of this testing process all the genes on the chromosome may be arranged in a definite linear order.

Double Crossovers. We note that the summation of the map distances between black and vestigial gives 18.5, but as shown by Morgan's experiments, using only black and vestigial, the crossing over between these two genes was 17 per cent The discrepancy is explained as the result of two simultaneous exchanges between the genes for black and vestigial, thus.



Although, as shown in the diagram, two crossovers have occurred between black and vestigial, these have produced no recombinations with respect to black and vestigial: one crossover has canceled the effect of the other. This case illustrates the fact that when two genes lie far enough apart for double crossovers to take place the frequency of observed recombinations is less than the frequency of chromatid exchanges Distances on the chromosome map tell us the expected frequency of recombinations only when the two genes are close to one another—so close that double crossovers do not occur.

Triple and other multiple crossovers also are known to occur Any even number of crossovers has the same effect as two; only odd numbers result in new combinations.

A Three-point Experiment. Let us now examine an experiment in which three genes in chromosome I of Drosophila (Fig 41) were studied simultaneously.[1] A female homozygous for the three recessive genes *ruby*, *cut*, and *vermilion*, *(rb ct v)(rb ct v)*, was crossed with a wild-type male. The F_1 triply heterozygous daughters were backcrossed to a triply recessive male ♀ *(Rb Ct V)(rb ct v)* × ♂ *(rb ct v)*. The females produced eight combinations in their eggs, as follows: *(Rb Ct V)*, *(rb ct v)*, *(Rb ct v)*, *(rb Ct V)*, *(Rb Ct v)*, *(rb ct V)*, *(Rb ct V)*, and *(rb Ct v)*. The male, of course, produced only one kind of sperm *(rb ct v)*. The F_2 offspring may therefore be listed directly from the above combinations in the eggs The following phenotypic ratio was obtained among the 1,622 F_2's.

Noncrossovers		Single crossovers			Double crossovers		
Rb Ct V	590	In the	Rb ct v	120	In both	Rb ct V	4
rb ct v	539	first	rb Ct V	137	regions	rb Ct v	11
(69 6%)	1,129	region	(15 9%)	257		(0 9%)	15
		In the	Rb Ct v	107			
		second	rb ct V	114			
		region	(13 6%)	221			

The recombinations resulting from crossing over between ruby and vermilion equal 478, or 29.5 per cent of the total This is the sum of the classes of single crossovers. There were 15 double crossovers. These show no new combinations between ruby and vermilion, and we would not know of their existence except for the presence of the gene *ct* lying between ruby and vermilion. We must conclude, however, that for each of the 15 double crossovers there was a simultaneous breakage in two regions of the chromosome, viz., between ruby and cut and between cut and vermilion. The actual crossovers in this experiment were therefore 257 + 15, or 272 (16 8 per cent), between ruby and cut, and 221 + 15, or 236 (14 5 per cent), between cut and vermilion, making a total of 508 crossovers among the 1,622 functional eggs, or 31.3 per cent.

We thus see that with two genes lying far apart, as with ruby and vermilion, the observed phenotypic recombinations between the two characters will be less than the sum of all the crossovers

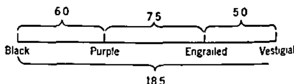
The authors state that in the experiment from which the above data were taken this is known to be all the crossing over that occurred, because

[1] T. H. Morgan, C. B Bridges, and A. H. Sturtevant, The Genetics of Drosophila, *Bibliographia Genet*, vol. 2, 1925.

In fact, no other sequence of these three genes in a straight line will fit the experimental results

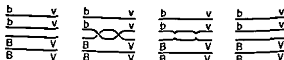
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Map Distances versus Chromosome Distances. Do the map distances as ascertained from recombination percentages represent accurately real distances on the chromosome? The evidence indicates that they do not. To quote Morgan on this point:[1]

> An important reservation must be made here—one that geneticists have always been aware of. We have assumed that the chance of crossing over is the same at every level of the chromosomes As will be shown presently this may be inexact The point is illustrated by a railroad timetable The time a train takes between stations is a fair measure of their distance apart, but it is not exact There may be grades or variations in speed, or waits at certain points in consequence of which the time between stations is not always an exact measure of their distance from each other So it may be with the map distances For, if crossing over should be more frequent in certain regions than in others, the map distances are only approximately true.

From observations of certain types of chromosome changes (Chap 12) has come the discovery that crossing over occurs with less frequency near the centromere at the center of the two long chromosomes of Drosophila than it does near the ends. The genes near the centromere are therefore actually farther apart on the chromosome than is indicated on the map

An important peculiarity respecting crossing over in Drosophila—a peculiarity which has made this animal an especially favorable one for the study of chromosome structure—is the failure of crossing over to take place in the male, under normal conditions The problem for the investigator is thus simplified in that he can determine directly the percentage of crossing over merely by observing the new combinations among the offspring, knowing that any new combinations must be the result of crossing over in the formation of the eggs.

SUMMARY

The number of genes possessed by an organism greatly exceeds the number of chromosomes. Ordinarily each chromosome contains many genes. Those in a single chromosome are said to be *linked*, and this principle of aggregation is known as *linkage*.

As a general rule the genes in a linkage group do not remain permanently linked, but may exchange places at meiosis with homologous genes on the opposite chromosome of the pair. This exchange is known as *crossing over*.

Linked genes cross over with a definite frequency in a uniform stock and under uniform environmental conditions

Individuals showing characteristics resulting from crossing over are

[1] Thomas Hunt Morgan, "The Scientific Basis of Evolution," W W. Norton & Company, Inc., New York, 1935.

known as *crossovers*, or *recombinations;* those in which no crossing over is evident are known as *noncrossovers.*

Genes cross over in chains, or segments, rather than singly. The exchanged chains of genes consist of homologous pieces of chromatids belonging to homologous chromosomes As a result of chromatid exchange two types of visible crossovers occur in equal numbers; likewise two types of noncrossovers occur in equal numbers

The frequency of crossing over between two genes depends directly, although not wholly, upon the distance apart the genes happen to lie upon the chromosome. In general the farther apart two genes lie, the higher is the percentage of crossing over.

The percentage of recombinations does not exceed 50 because (1) double crossovers, triple crossovers, etc , occur between two genes that are far apart, (2) only single and other odd-numbered crossovers between these two genes result in recombination; and (3) only two chromatid strands break and rejoin at any one level.

By comparing mutual crossover percentages, linked genes may be graphed on a single straight line Such a graph is known as a *chromosome map.* The gene loci are separated on the map by distances corresponding to their crossover percentages. Because of the existence of double and multiple crossovers the map is accurate only for genes relatively close together Discrepancies between map distances and actual chromosome distances sometimes occur as a result of differentiation within the structure of the chromosome. For example, in Drosophila and in some other organisms a special kind of chromatin known as heterochromatin is concentrated near the centromeres of the chromosomes. Crossing over is relatively infrequent near the centromeres Moreover, a crossover tends to inhibit the occurrence of another crossover nearby; this is known as *interference*

Linkage is an incidental result of the aggregation of genes in chromosomes Its effect is to limit the variability among individuals Crossing over, on the contrary, has the effect of increasing variability. If linkage were complete, i.e., if there were no crossing over, there would be, effectively, only as many series of alleles as chromosomes, since each chromosome possessing a mutant at any locus whatsoever would behave merely as an allele of its homologous chromosome that lacks that *mutant* Thus two new mutations at different loci in a given chromosome would add only two new combinations for this chromosome, making a total of three. the original $\underline{A \quad B}$ and mutants $\underline{A \quad b}$ and $\underline{a \quad B}$. With crossing over there would be 2^2, or four, combinations possible: $\underline{A \quad B}$, $\underline{A \quad b}$, $\underline{a \quad B}$, and $\underline{a \quad b}$ For the same reason, 100 mutations at different loci in a particular chromosome would give only 101 combinations for this chromosome, in the absence of crossing over, but 2^{100} possible combinations with crossing over

This latter huge number also represents, of course, the number of possible combinations with 100 genes on as many separate chromosomes assorting independently.

With respect to the evolutionary significance of linkage and crossing over there are probably advantages to the species both in the possibility of recombination and in some restraint on the freedom of recombination, and the situation actually found in a species is the result of a process of selection toward the most favorable balance.)

PROBLEMS

Caution In working problems in linkage always keep the symbols for linked genes together, in gametes as well as in zygotes, by enclosing them in parentheses, instead of bringing pairs of alleles together as in independent assortment

1. In Drosophila the percentage of crossing over between vestigial and lobe (an abnormal eye character) is 5 0 per cent Vestigial is recessive, lobe is dominant Diagram the results of a mating between a male homozygous for lobe and long wing, and a normal-eyed vestigial female; follow this by a backcross of one of the female offspring to a normal-eyed vestigial male, showing the expected phenotypic ratio among the offspring of the backcross mating

2 Show the ratio resulting from a mating between a male and female both obtained in the first cross in Problem 1. (No crossing over in males of Drosophila)

3 Crossing over in Drosophila takes place between lobe and engrailed (an abnormal recessive body character) with a frequency of 10 0 per cent Determine the ratio from a mating between a female heterozygous for both lobe and engrailed, and a normal-eyed engrailed male $(L\ E)(l\ e) \times (l\ e)(l\ e)$

4. Show the results of a mating between a male and a female both heterozygous for lobe and engrailed, $(L\ E)(l\ e) \times (L\ E)(l\ e)$

5 Calculate the phenotypic ratio expected from the following cross ♀ $(L\ e)(l\ E) \times$ ♂ $(L\ E)(l\ e)$

6. As noted above, lobe and vestigial have a crossover frequency of 5 0 per cent, lobe and engrailed a frequency of 10 0 per cent; while vestigial and engrailed cross over with a frequency of 5 0 per cent. Arrange these three genes on a chromosome map.

Note In corn, a recessive gene *c*, known as colorless, eliminates all color from the seed Seeds with the dominant gene *C* are colored. A recessive known as shrunken, *s*, causes the seed to be dented or shrunken, seeds with the allele *S* are full The genes mentioned cross over with a frequency of 3 0 per cent Crossing over occurs in both the male and the female parts of the plant.

Show the results of the following matings:

7. Colored full, $(C\ S)(c\ s) \times$ colorless shrunken, $(c\ s)(c\ s)$.

8 Colored full, $(c\ S)(C\ s) \times$ colorless shrunken, $(c\ s)(c\ s)$

9 Colored full, $(C\ S)(c\ s) \times$ colored full, $(C\ S)(c\ s)$

10 What is the chance that two genes chosen at random in peas (7 pairs of chromosomes) will be linked? What is the chance in man with 24 pairs of chromosomes? In both species assume that the genes are equally distributed among the chromosomes

Note In rabbits the *Dutch* type of white spotting, (*d*), similar in appearance to the white spotting in guinea pigs, is recessive to self color Long hair, or *Angora*, (*l*), is recessive to the normal short hair. The genes *d* and *l* are linked, with a crossover percentage of about 14 0. Show the phenotypic ratios expected from the following crosses:

11. A hybrid (obtained from a cross between a Dutch, Angora, and a homozygous self, short hair) × a Dutch, Angora

12. A hybrid (obtained from a cross between a Dutch, homozygous short hair, and a homozygous self, Angora) × a Dutch, Angora

Note In guinea pigs Sewall Wright found good evidence that the gene for roughness (*R*) is linked with the gene for the restoration of the missing thumb, or pollux, (*Px*) These genes show crossing over in about 42 per cent of the gametes Calculate the expected phenotypic ratios in the following matings—crossing over is present in both sexes

13. (*R Px*)(*r px*) × (*r px*)(*r px*).

14 (*R px*)(*r Px*) × (*r px*)(*r px*)

15. In guinea pigs there are 32 pairs of chromosomes What is the chance that eight genes chosen at random will all be on separate chromosomes? Show your method of calculation

16 In Drosophila two recessive genes in chromosome III, *scarlet* and *dwarf*, show 6 0 per cent crossing over Calculate the expected ratio from a doubly heterozygous female, (*D S*)(*d s*), with a male, (*d s*)(*d s*) The normal alternatives of *scarlet* and *dwarf* are *red* eye and *normal* body, respectively

17. Calculate the expected ratio from a mating of F_1 flies obtained from the parental cross (*d S*)(*d S*) × (*D s*)(*D s*). (No crossing over in males)

18. In Drosophila the genes for vestigial and safranin (both recessives in chromosome II) show 7 0 per cent crossing over. Calculate the expected ratio from a doubly heterozygous long-winged red-eyed female mated with a vestigial safranin male (*v S*)(*V s*) × (*v s*)(*v s*)

19 Calculate the expected ratio from a mating between a female and a male, each of the constitution (*v S*)(*V s*) (No crossing over in male Drosophila)

20 In a mating between a triple heterozygote, (*A B C*)(*a b c*), and a triple recessive, (*a b c*)(*a b c*), there were 1,000 offspring made up of the following phenotypes (using roman letters to represent phenotypes):

A B C	428	A B c	44
a b c	420	a b C	38
A b c	34	a B c	1
a B C	33	A b C	2

Calculate the number of recombinations between a and b, b and c; a and c How do you account for the fact that the sum of the first two exceeds the last? Calculate *coincidence*

9

SEX DETERMINATION AND SEX DIFFERENTIATION

As a result of investigations made since the resurrection of Mendel's paper, we now know that sex is a characteristic which follows the law of segregation. Mendel himself, in a letter to the botanist Nägeli, in September, 1870, had suggested this as a possibility. The final solution of the problem of sex determination was, in fact, a logical outgrowth of the discovery of Mendel's first law.

The importance of sex in the biological world, including the world of human affairs, can hardly be overestimated Since ancient times men have speculated on the causes of sex differences, and the great number of earlier theories revolving around sex goes to show how inadequate these theories proved to be.

Before the mechanism of heredity became known, the theories of sex determination usually emphasized the *external* environment rather than the *inherent* nature of the reproductive cells Thus, at various times, it had been maintained that the sex of the child was determined by the relative vigor of the parents, by their relative ages, by the nutrition of the mother, by the season of mating, by the ripeness of the egg (time elapsed between the release of the egg from the ovary and its fertilization by the sperm), by the particular ovary or testis (right or left as the case may be) which produced the egg or sperm, etc. None of these environmental factors, however, had stood the test of critical examination. Therefore, investigators finally turned their attention to the internal mechanism of the cell, where eventually they found the true explanation.

CHROMOSOMES AND SEX DETERMINATION

The first definite suggestion of a chromosome mechanism for the determination of sex came from Professor C. E. McClung, an American zoologist, who observed in 1902, while studying the cells of grasshoppers, that one of the chromosomes of the male always lacked a mate. The male thus

Upon examination of the cells of many animals, the foregoing type of chromosome arrangement was found to be a very common one, especially in certain insects and nematode worms.

In 1905 Wilson described a slightly different type of chromosome arrangement in a number of other insects; namely, a condition in which both sexes had the same *even number* of chromosomes, the female having two X's and the male one X paired up with a much smaller "Y" The sexes in such cases are therefore designated XX = female, XY = male Wilson regarded this as the more primitive condition, from which the XO condition had evolved Obviously, a gradual reduction in the size of the Y chromosome in a species and its final complete elimination would result in the XO condition

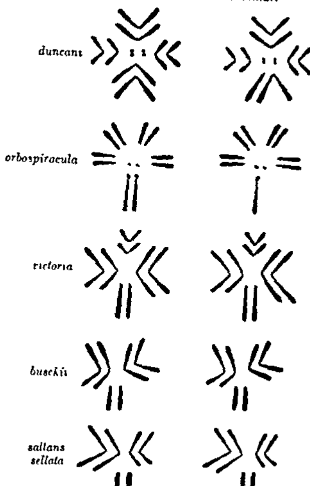


Figure 50. Semidiagrammatic drawings of the chromosomes in the metaphase plate stage in six species of the genus *Drosophila*. Chromosomes of females are shown on the left and males on the right. X and Y chromosomes are placed at the bottom of the diagram in each case. The lower figure serves for two species. In *D. duncani* the Y chromosome is a straight rod and the X chromosome is V-shaped, in *D. orbospiracula* the male has no Y chromosome, and in the other four species the X and Y chromosomes are visibly alike. (*From Patterson, Studies in the Genetics of Drosophila, III. The Drosophilidae of the Southwest, Univ. Texas Publ.* 4313.)

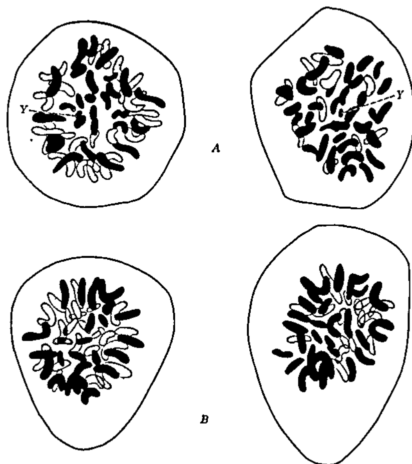


Figure 51. Human chromosomes (*A*) Male: metaphase plate stage of spermatogonia from two different men, each cell showing 48 chromosomes. The smaller chromosomes typically are arranged in the center of the cell × 3,600 diameters (*B*) Female metaphase plate stage in two cells from the uterus, each cell showing 48 chromosomes × 3,600 diameters (*C*) Male (*D*) Female. Chromosomes from somatic prophase nuclei, arranged in pairs according to size The X and Y chromosomes of the male are shown at the extreme right. (*From Evans and Suezy, The Chromosomes in Man, Sex and Somatic, Mem Univ. Calif*, *vol.* 9, *no.* 1, 1929.)

the development of a female In some way these original quantitative differences subsequently give rise to the qualitative differences between the sexes.

In most animals and plants with separate sexes so far investigated, sex has been found to depend upon a difference in the chromosomes of the male, as already described. Interesting exceptions exist in the case of birds and certain moths, fishes, amphibians, and reptiles, in which the female rather than the male is heterozygous for sex In some of these the female has but one X chromosome and no Y, and the male has two X's, and in others the female has an X and a Y and the male has two X chromosomes. The end result is identical, however, so far as the sex ratio is concerned, since with two kinds of eggs produced in equal numbers and only one kind of sperm, males and females will appear in equal numbers just as in the more numerous species whose males are heterozygous for sex.

SEX RATIO IN MAN AND ANIMALS

How is the chromosome theory of sex determination actually borne out by birth records in man and other species? According to records compiled by Professor Jay L. Lush,[1] of Iowa State College, the sex ratio at birth (expressed in percentages of males among all births) for man and some of the common domesticated mammals is as shown in Table 9 In most cases the ratio is based upon many thousands of births Some of the variation within a species is probably due to actual differences among breeds or races.

TABLE 9 SEX RATIO AT BIRTH

Species	*Males, %*
Man	50 7–51 7
Dog	51 5–52 8
Rat	51 2
Mouse	50 0–54 1
Pig	50 1–52 3
Cow	49 4–52 2
Horse	48 9–49 9
Mule	44 3
Sheep	49 0–49 5
Goat (Angora)	50 1
Rabbit	51 1

The deviation from the expected ratio of 1 1 in man, although not great, is highly significant and not due to errors of sampling, since it is based upon millions of births, and is true for the human species in general

[1] Jay L Lush, "Animal Breeding Plans," 3d ed , Iowa State College Press, Ames, Iowa, 1945.

all over the world. This is illustrated in Table 10 showing some of the countries in which relatively accurate birth statistics have been kept

What is the cause of the excess of male births over female births in man? One of the most natural explanations that might occur to the reader would be a differential mortality of the two sexes operating against the females prior to birth All the evidence available, however, leads to the opposite conclusion It is the male sex which suffers the higher prenatal mortality This has been proved by a number of studies of the sex of premature births including embryos as young as four months and less The greatest excess of stillborn males is found in the youngest groups Strandskov and Bisaccia[1] made a thorough study of the stillbirths in a restricted region of the United States where early as well as late stillbirths are reported for the years 1922–1936 The total number of births, including stillbirths, was 7,723,922, of which 51 31 per cent were males The stillbirths are shown in Table 11 The percentage of male stillbirths decreases with age until the seventh month, then rises somewhat

TABLE 10 HUMAN SEX RATIO AT BIRTH, 1921–1925*

Country	*Males, %*
Germany	51 6
Finland	51 5
Sweden	51 4
United States†	51 4
Netherlands	51 4
Norway	51 3
Italy	51 3
Scotland	51 2
Belgium	51 2
France	51 2
Switzerland	51 2
England and Wales	51 1
Japan (1921–1924)	51 0

* S Jastrzebski, Sex-ratio at Birth and Death, "Encyclopaedia Britannica," 14th ed

† Report of U S Bureau of the Census (In 1921 there were 24 states, chiefly in the South and West, which were not included in the birth-registration area; 10 of these were added in the period 1921 to 1925, and in 1933 the last one, Texas, was added)

If the same rule of excess mortality in male embryos holds in the still younger aborted embryos, which are not ordinarily observed, and so on, all the way back to fertilization, we are left with the necessity of concluding that a higher percentage of fertilizations must be effected by sperms carrying a Y chromosome than by sperms carrying an X chromosome The existence of such a differential fertilization has not been proved, but

[1] H. H. Strandskov and H Bisaccia, The Sex Ratio of Human Stillbirths at Each Month of Uterogestation and at Conception, *Am. J. Phys Anthropol*, n.s, 7:131–143, 1949

it is the most probable explanation so far offered. Several hypotheses have been proposed to account for such a supposed differential fertilization. T. H. Morgan[1] suggested that since the Y chromosome in man is only about one-half the size of the X chromosome, the head of the sperm carrying the Y chromosome may be slightly smaller, hence the Y-carrying sperm should have a slight advantage in the long race up the uterus and oviduct of the female to the upper end of the oviduct where fertilization is effected.

TABLE 11. STILLBIRTHS FOR WHICH SEX AND MONTH WERE REPORTED FROM A RESTRICTED AREA OF UNITED STATES*
(Data from U S. Bureau of the Census, 1922–1936, inclusive)

Month of uterogestation	Total no. of stillbirths	No of male stillbirths	Mean of the 15 yearly percentages of male stillbirths
Under 4th	4,519	3,539	78 610
4th	9,408	6,289	67 065
5th	18,207	10,627	58 571
6th	26,021	14,341	55 089
7th	33,513	17,923	53 529
8th	42,151	23,282	55 204
9th	99,054	56,909	57 324
10th	3,707	2,135	57 841
Total period	236,580	135,045	57 078

* After Strandskov and Bisaccia.

In conformity with this hypothesis it is reported that two sizes of human sperms actually exist In a number of animals, including the pig, the dog, the horse, and the worm *Ascaris*, measurements of the sperm heads (largely chromatin) have been made and the dimensions plotted in curves of variability. According to Wilson,[2] "in nearly all cases the curves have been bimodal, indicating the existence of two size-groups" In man also, two classes of sperms, based on size differences, have been reported [3] Some investigators, however, have questioned whether the differences in size of sperm are due to differences in chromosome content Differences in maturity of the sperms have been suggested as a cause The problem seems to call for further research.

No one has yet been able to separate experimentally the X and Y sperms, although the attempt has been made using several methods such

[1] T. H. Morgan, "The Physical Basis of Heredity," J B Lippincott Company, Philadelphia, 1919.

[2] Wilson, *op cit*

[3] A. S Parkes, Head Length Dimorphism of Mammalian Spermatozoa, *Quart. J Microscop. Sci*, 67 617–625, 1923.

as centrifuging and electrolysis. Nor have there been any dependable successes in controlling the sex in mammals by the use of chemicals introduced into the female genital tract prior to mating, although this has been tried, using acids and alkalies. A reliable means of controlling the sex of offspring would be of great practical importance in breeding domesticated mammals (dairy cattle, for example), to say nothing of the effect it might have upon the human population.

There are racial differences in sex ratio. Negroes in the United States have a lower proportion of males to females than do whites. According to the Bureau of the Census, in the United States in 1949 there were 3,083,721 living white births reported, of which 51.43 per cent were males. In the same year there were 453,235 living Negro births, of which 50.54 per cent were males Whether this difference in the races—which is not very great, although unquestionably significant—is due in whole or in part to hereditary differences, hence truly racial, or to environmental differences has not been determined

It seems well established that differences in heredity may modify the expected 1 1 sex ratio in mammals The most extensive experiments on this point are those of Helen D King,[1] who developed by inbreeding and selection two families of rats which differed strikingly in their sex ratio: 55 6 per cent males in one family and 45.4 per cent in the other. Although the difference between the two families of rats is obviously hereditary, the environment having been the same for both, the way in which the genes affect the ratio is not known.

TWINS: CAUSE AND SEX RATIO

The discovery that sex is inherited in a manner analogous to ordinary Mendelian traits has opened the way to the solution of the problem of human twins Everyone is interested in twins—especially identical twins—but until the mechanism of sex determination was known no one could explain them Twins are of two types—identical and fraternal—and each type results from a quite different cause.

Fraternal twins may be of the same or of opposite sex They have no more in common than brothers and sisters born to the same parents at different times excepting the slight effects which may come from sharing the same uterine home during the nine months of their embryonic life. The explanation of fraternal twins is that two eggs happen to be released from the ovary or ovaries at the same time, instead of the usual single egg; each egg is then fertilized by a separate sperm. Such twins are therefore designated two-egg, or dizygotic, twins Plural births of this type, whether

[1] Helen Dean King, "Studies on Inbreeding," (reprinted from *J Expt. Zool*, vols 26, 27, and 29), Wistar Institute, Philadelphia, 1919.



Figure 52 A pair of attractive and strikingly similar identical twins. Facial features and other physical traits—coloring, body build, etc.—are practically indistinguishable. They are alike also in aptitudes, interests, voice, and personality. (*Photographed by the author during twins' second year in college.*)

twins, triplets, quadruplets, quintuplets, or sextuplets, are in exactly the same category as plural births in many of the other mammals, in some of which, especially the smaller mammals, plural births are the rule. There seem to be no reliable records of more than six children being born to human parents at one time.

Twins of the other type, known as identical twins, are always of the same sex, and in other respects are so much alike that they are often distinguished with difficulty by friends, relatives, and even parents Such twins are derived from a single egg, hence are called one-egg, or monozygotic, twins. The twin girls, college students, whose photographs are shown in Fig 52, are examples of a pair of extremely similar identical twins Identical twins are sometimes more alike than the opposite sides of a single individual, and, significantly, this is true of such highly individual characteristics as fingerprint patterns.

From what we know of heredity, we conclude that identical twins are identical because they have identical sets of genes. On the basis of the large number of chromosomes and genes in man we have already seen how improbable it is that any two fertilized eggs, even from the same parents, would ever possess identical sets of genes. As a practical matter, the only way two identical sets of genes ever arise in nature (in biparental organisms at least) is through mitotic cell division such as occurs in embryonic development and growth. If in early embryonic development, before differentiation has taken place or organs have been laid down, the embryo could be separated into two halves, these might develop into two identical individuals. This appears to be exactly what happens in the production of identical twins.

Identical twins have been produced experimentally in lower animals by various methods, including the tying of a fine hair around a newt embryo in the two-cell stage in such a way as to separate the two cells, by lowering the temperature; or by reducing the oxygen supply in the case of developing fish eggs, thus causing twin embryos to develop from one egg

Because of the difficulties in observing early development in human beings, the complete visual proof of the origin of identical twins in man from a single egg has not been obtained In one mammal, however, the proof is available. the mammal referred to is the nine-banded armadillo of Texas (Fig 53). In 1909 two American zoologists, H. H. Newman and J. T. Patterson, discovered that the armadillo habitually produces a litter of four (quadruplets); that the members of any given litter are always of the same sex, and that the members of any one litter are usually strikingly alike (Fig. 54). This discovery was followed by a series of papers in one of which Newman[1] showed that in armadillos only one egg—a typical mam-

[1] H. H. Newman, "The Physiology of Twinning," University of Chicago Press, Chicago, 1923 (Contains a summary of the armadillo studies)

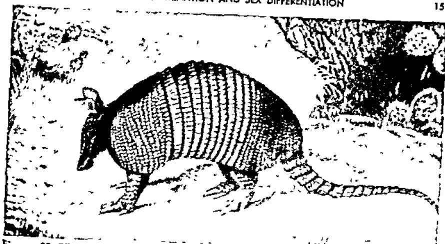


Figure 53. The nine-banded armadillo of Texas (*Dasypus novemcinctus*), showing the animal in its native habitat. (*From Newman, "The Biology of Twins," University of Chicago Press.*)

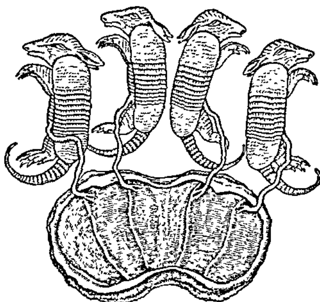


Figure 54. Identical armadillo quadruplets in the embryonic stage, shown removed from their common membranes. The nine-banded armadillo produces quadruplets at each birth; all four are of the same sex and come from a single fertilized egg. (*From Newman, "Outlines of General Zoology," The Macmillan Company.*)

malian egg—is released from the ovary at each breeding. On the basis of these studies Newman formulated a theory as to the cause of the division of the early embryo into four independent embryos He suggested that a lowering of the rate of metabolism resulted in the "physiological isolation of parts at certain distances from the dominant (apical) region. When such isolation occurs new centers of control arise, which produce buds capable of establishing whole new systems like the original."

In 1913 Patterson added the final visible proof of the origin of the quadruplets by observing a number of embryos in pre-twinning stages, as well

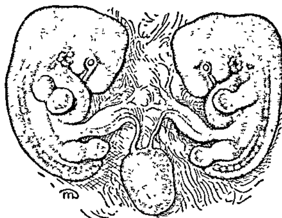


Figure 55. Twin human embryos (12 mm. in length and about six weeks of age), each with its own umbilical cord and yolk stalk, but with common yolk sac and placenta. Both embryos probably developed from a single egg. (*From Arey, "Developmental Anatomy," W. B. Saunders Company.*)

as in many stages of twinning which showed the four embryos arising from a single egg It was discovered also that in the early pre-twinning stages the embryos were very slow in establishing connections with the uterine wall As pointed out by Newman, this delay would result in an arrest of development, with the subsequent twinning

Whether a similar situation exists in man in the case of identical twins, triplets, and other multiple births has not been discovered, but it is probable that the conditions are essentially the same as in the armadillo This probability is supported by the discovery of a few early human twin embryos showing certain characteristics comparable to those observed in armadillo quadruplets (Fig. 55). In human beings the early embryo requires several days to become implanted in the uterine wall after it has reached the uterus It is probable that in the case of some human embryos, for one reason or another, there is an undue delay in implantation,

with a result similar to that in the armadillo, except that in man there are usually only two embryos instead of four

Identical triplets, quadruplets, quintuplets, and even sextuplets occasionally occur in man According to Professor John W MacArthur,[1 2] of the University of Toronto, and others who have studied the Dionne quintuplets, after application of all the known tests for identical and fraternal twins, there is no doubt that all five girls came from a single fertilized egg. There is good evidence, according to Dr Dafoe,[3] that there were originally six embryos, the sixth having aborted very early

In man, besides the evidence from the study of twins themselves, and argument from analogy with other animals, we have convincing supplementary evidence for the existence of one-egg twins this evidence has to do with the sex ratio of twin births For example, in 1950, in the United States, there were born 38,705 pairs of twins, including stillbirths [4] This is about one twin birth in each 97 births The twins were distributed by sex as follows.

2 males	13,440
1 male, 1 female	12,532
2 females	12,733
Total	38,705

Note that this is close to a 1.1:1 ratio of the three possible combinations of the sexes. Let us suppose that each of these pairs of twins came from two separate fertilized eggs, i e , that they are all fraternal twins What then would be the expected ratio of the three combinations? Obviously it would be quite different from the numbers above With separate eggs, each fertilization is an independent event, and the ratio of the three possible combinations of sexes in the twins (ignoring for the moment the small excess of male births) will be 1 (2 males) 2 (1 male and 1 female):1 (2 females) This ratio is an illustration of the law of probability, which states that the chance of the simultaneous occurrence of two independent events is equal to the product of the chances of the separate occurrence of the events If one-half of all births are male births, two males should occur in ½ × ½, or ¼, of twin births For the same reason two females should occur in ¼ of the twin births, leaving ½ of all twin births as one male and one female The truth of the law here illustrated may be verified readily

[1] J W MacArthur, Genetics of Quintuplets I Diagnosis of the Dionne Quintuplets as a Monozygotic Set, *J. Heredity*, 29:322-329, 1938

[2] W. E. Blatz et al, "Collected Studies on the Dionne Quintuplets," University of Toronto Press, Toronto, 1937

[3] A. R. Dafoe, The Dionne Quintuplets, *J. Am. Med Assoc*, 103:673-677, 1934.

[4] From data furnished by the National Office of Vital Statistics, *Public Health Service*, Washington Cases of plural fetal deaths are included only if the period of gestation was given as 20 weeks (or 5 months) or more, or was not stated

by tossing simultaneously two coins In 100 throws there will on the average be 25 (2 heads) 50 (1 head, 1 tail):25 (2 tails)

But the birth statistics cited above show a ratio very close to 1·1·1 instead of 1·2·1 The same-sexed twins are obviously much too numerous, if we assume that each individual is derived from a single fertilized egg; and with numbers as large as these, the discrepancy cannot be due to a mere chance deviation If all twins were fraternal twins, the expected numbers in each combination (assuming a sex ratio of 1:1) would be as indicated in the second line of Table 12.

TABLE 12 TWIN BIRTHS IN THE UNITED STATES FOR 1950

	Two males	Male and female	Two females
Pairs of twins born, including stillbirths	13,440	12,532	12,733
Expected if all twins were fraternal (1♂ 1♀)	6,266	12,532	6,266
Expected fraternal twins (50 9% ♂'s·49 1% ♀'s)	6,379	12,532	6,153
Excess of same-sexed twins (probably identical)	7,061		6,580

From the figures cited we see that there were roughly twice as many same-sexed twins as there should have been had each individual originated from a single fertilized egg—in other words, about half of all same-sexed twins must have been identical (one-egg) twins This conclusion seems to agree very well with the actual diagnosis of twin types; for according to Professor H. H Newman, leading student of twins in this country, the numbers of identical twins and same-sexed fraternal twins in the population are about equal.

According to the above calculations, 35.2 per cent of all twin births in the United States for 1950 are classed as identical. A comparison of the statistics for whites and nonwhites (almost entirely Negroes) discloses an interesting racial difference in the proportion of fraternal and identical twins· in twins classed as "white" 36 8 per cent are identical, while in "other races" only 27 6 per cent are identical This lower percentage of identical twins in Negroes is due to the much higher frequency of fraternal twins among the total Negro births Identical twins occur about as frequently among Negroes as among whites.

"Siamese" Twins and "Double Monsters"

Twins are occasionally born physically joined one to the other. The extent of the union varies from a superficial one permitting their ready separation, to a union so deep-seated that life is not possible. Surviving conjoined twins usually find their way eventually into the circus or vaude-

ville shows, as did the famous original Siamese twins of the nineteenth century, who toured the country on exhibition for many years

Conjoined twins are probably always of the one-egg variety in which separation, for some unknown reason, stopped short of completion They are always of the same sex, and otherwise give evidence of having come from a single egg; although, for reasons given in Chap 11, they are usually less alike than separate identical twins Corresponding parts are united, with the result that the twins are joined symmetrically with respect to one another. If the union results in a highly abnormal condition, for example, a single head and a double body, or two heads and a single body, they are popularly known as "double monsters." These extremely abnormal specimens usually do not live In ancient times various superstitious beliefs grew up around double monsters, some people even maintained that they were the hybrid offspring of man with some other mammal. As a matter of fact, there is no evidence of the origin of a hybrid between man and any other mammal

Heredity of Twinning in Man

Numerous statistical studies show striking differences in the frequency of two-egg twins among families and races These differences seem to be hereditary, but the exact mode of inheritance is unknown Since two-egg twins come from eggs released from the ovary at the same time, we might expect that only the mother could be given credit for the birth of two-egg twins Some studies, in fact, so indicate, but in one report both mothers and fathers of such twins belong to pedigrees with high rates of twinning [1] How the father could play a part in two-egg twinning is unknown

There is little evidence for any hereditary differences with respect to the production of one-egg twins No racial differences exist in this respect so far as known.

Various independent studies of birth statistics in this country and abroad demonstrate that the age of the mother is a very important factor in the production of two-egg twins, but of little or no importance in the production of one-egg twins Stocks[2] has made an analysis of births in England and Wales from mid-1938 to 1947. The total number of births, 6,620,794, includes 81,133 pairs of twins. The frequency of twin births per 1,000 "maternities," i e , confinements resulting in birth of one or more live or stillborn children, among the legitimate births, according to the age of the mother and type of twins, is shown in Table 13

[1] W. W Greulich, Heredity in Human Twinning, *Am J. Phys Anthropol*, **19**:391–431, 1946

[2] Percy Stocks, Recent Statistics of Multiple Births in England and Wales, *Acta Genetica Medicae et Gemellologiae*, **1**:8–12, Rome, 1952

TABLE 13. EFFECT OF AGE OF MOTHER ON FREQUENCY OF TWIN BIRTHS*

Average age of mother in years	One-egg twins per 1,000 births	Two-egg twins per 1,000 births
19	3 05	3 30
22 8	3 23	5 26
27 5	3 31	7 91
32 3	3 51	10 82
37 2	3 86	12 79
41 8	3 55	9 47
46 3	4 29	2 61

* From Stocks

These data show a pronounced effect of age of mother on frequency of two-egg twins, but no more than a slight effect on frequency of one-egg twins For the illegitimate births there was a similar effect of age of mother on two-egg twinning, but no effect at all on one-egg twinning. Stocks concludes that age of mother has little or no effect on one-egg twinning.

SEX DIFFERENTIATION

The differentiation of the sexes in man is a gradual process involving a long chain of cause and effect As we have already seen, the primary factor is a difference in the chromosomes, two X chromosomes producing a female and an X and a Y a male The first indication of sexual differentiation is in the gonads. Up to about six weeks of embryonic development, at which time the embryo is about 12 mm in length (Fig. 55), the sexes cannot be distinguished, the gonads of both sexes look alike At about 13 mm the male shows the first signs of differentiation, and at this time the gonads are recognizable under the microscope as developing testes The gonads of the female embryo remain indifferent in appearance for about one week longer than those of the male, and then begin a process of differentiation into ovaries.

One of the characteristic differences between the sexes of adults is in the ducts used for carrying sperms and eggs to the exterior. Before the gonads differentiate, each sex develops both male and female ducts; with the differentiation of the gonads into testes or ovaries, the ducts of the opposite sex degenerate The stimulating factor in this degenerative process seems to be the hormones secreted by the testes and ovaries.

The external genitalia begin their development during the sixth week of embryonic life, but for a week or more are alike in both sexes By the end of the seventh week sex may be distinguished—though with some uncertainty—by external differences. Differentiation proceeds, and by the

twelfth week the external genitalia in each sex have become clearly distinguishable and fairly characteristic

After birth other sexual differences not directly a part of the reproductive system, and hence known as secondary sexual characters, gradually appear. These differences are not particularly marked until sexual maturity approaches The arrival of sexual maturity, known as puberty, or the beginning of the period of adolescence, is associated with the sudden increase in secretion of hormones by the gonads and some of the other glands of internal secretion. One effect of the hormones is a difference in the rate of metabolism in the two sexes At five years of age the rate in males is about 3 per cent above that of females, this difference rises to about 12 per cent at 16 years and falls gradually thereafter Associated with the difference in metabolic rate is the tendency of the female to store up a larger amount of energy in the form of fat

Since the gonad hormones are a necessary link in the differentiation of sexual characters, it is natural that anything which causes a destruction or removal of the gonads should result in a profound modification of sexual development Removal of the testes before sexual maturity, as formerly practiced in the production of eunuchs, results in striking effects Masculine characters fail to develop normally, and the eunuch retains some of the neutral characters found in preadolescent children The voice remains high-pitched, resembling that of the female, the beard fails to develop, and fat is deposited in unusual amounts

If normal development is interfered with either by genes or by some environmental factor, prior to birth, there may result what is known as a hermaphrodite. True hermaphroditism (from the Greek god Hermes and the goddess Aphrodite) refers to that condition—normally present in many lower animals, including some vertebrates—in which sperms and eggs are produced by the same individual. This is extremely rare in man, although actual cases have been reported. There is no proof that such an individual can function both as a father and as a mother The internal genitalia are imperfectly developed, while the external genitalia show mixed male and female characteristics The secondary sexual characters such as beard, mammary glands, and voice are intermediate

Most so-called hermaphrodites display false hermaphroditism, i.e , the gonads are of one sex only, while the external genitalia are of intermediate type. Technically they are known as intersexes The internal genital tract also is intermediate or mixed in type In male false hermaphroditism the testes are often undescended, while the external genitalia resemble somewhat those of the female This is due to an arrest of development, including hypospadias (Chap 16) Such an individual, as a child, may for a time be considered a female, but with the onset of adolescence the increase in male hormones suddenly causes the child to develop male secondary sex

characters This is the type of case that is sometimes wrongly described in the popular press as an example of sex reversal.

In female false hermaphroditism ovaries are present and sometimes descended, in position they resemble the testes in the male, while the external genitalia tend in the male direction. This type of individual may be taken for a male during early childhood; at puberty suddenly it may seem to be transformed into a female Obviously, cases of male and female false hermaphroditism are not to be regarded as sex reversals. There is no proof that true sex reversal—the conversion of an individual of one sexual genotype into a functional individual of the other sex—ever occurs in man or in any other mammal Sex reversal seems to be incompatible with the peculiarities of uterine development possessed by mammals, including the highly standardized temperature and nutritional conditions Furthermore, the fact that a complex genital apparatus differentiates early in embryonic life in mammals makes sex reversal during late embryonic stages impossible, because once differentiation of sex has proceeded very far in either direction, there can be no retracing of the steps.

Freemartins. It is possible to have an interference with the normal hormone conditions during embryonic life in mammals of such a nature as to produce false hermaphroditism, or intersexuality. A well-known case of this type occurs naturally in cattle twins. Most cattle twins arise from two separate eggs They may consist of two males, two females, or a male and a female. When both twins are of the same sex, development proceeds normally, but when one is a male and the other a female, it is found in a large percentage of cases that the female is an intersex. The external genitalia are of female type while the internal organs resemble the male The male, on the contrary, is always normal Such abnormal females are known as freemartins, they are always sterile.

In 1916, Professor F R Lillie, of the University of Chicago, taking advantage of the abundant material available at the Chicago stockyards, examined many pairs of cattle twin embryos in an attempt to discover the cause of freemartins in cattle. On examining the twin embryos he found that there was usually a fusion of the embryonic membranes and embryonic blood vessels of such a nature as to permit the blood from one embryo to pass directly to the other (Fig. 56). Whenever such fusions took place the female of the pair of twins of unlike sex was always damaged in that its sex organs were modified in the male direction. In those rare instances involving no fusion of the blood vessels, the female developed normally. Since the sex hormones constitute the only known difference between the blood of the male and that of the female, and since the testes develop ahead of the ovaries, it was assumed that the male hormone was responsible for the partial sex reversal of the female.

This theory has recently been called into question by Professor Carl R

Moore, of the University of Chicago,[1] who doubts that the embryonic testis is secreting hormones at this early stage In his opinion the responses of the duct system in the freemartin are not yet duplicated by any experimental treatment in mammals He agrees that a chemical substance transported through the blood stream is the effective agent, but doubts that the substance is of the true sex-hormone type He offers the suggestion that a difference in chemical substances produced by the body cells in general of males and females, rather than the testis specifically, may be the explanation of the freemartin.

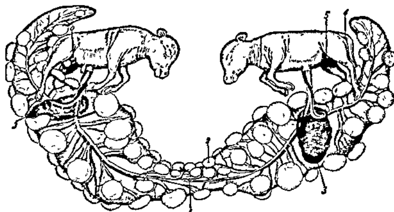


Figure 56. A typical opposite-sexed pair of cattle twins, male on the left and freemartin on the right, showing. (1) The connecting artery between the two twins. (2) A single placental cotyledon entered by veins from both embryos. (3) Opening into the chorion through which the embryos have been removed (4) Clitoris of the freemartin (5) The well-separated anterior and posterior teats characteristic of the female (6) The much closer teats characteristic of the male. (*From Newman, "Outlines of General Zoology," 3d ed., The Macmillan Company, after Lillie*)

There is no evidence that intersexes in man are ever caused by a mingling of blood in twins as in freemartins in cattle According to Professor Newman, there are no known cases of two-egg twins in man involving fusion of fetal blood vessels.

True Hermaphroditism. The problem of the cause of intersexes and of true hermaphroditism in man has not been solved No environmental factor is known that can be held accountable, and by analogy with certain insects (the moth *Lymantria* and the fruit fly *Drosophila*) it is quite possible that genes are responsible. A H Sturtevant,[2] of the California Insti-

[1] C. R Moore, Gonad Hormones and Sex Differentiation, *Am Naturalist*, 78:97–130, 1944.

[2] A H. Sturtevant, A Gene in *Drosophila melanogaster* That Transforms Females into Males, *Genetics*, 30:297–299, 1945

tute of Technology, discovered a gene in *Drosophila melanogaster* that transforms females into males. The gene is a recessive, lying between 44 and 45 3 in chromosome III (Fig 41, page 123). The transformed females are indistinguishable from normal males except for their sterility, a reduction in testis size, and apparently an approach to the body size and the development rate of females The gene has no effect on normal males

Of special significance in mammals is the fact that in goats the intersexual condition seems to be inherited as a simple recessive.[1] It is probable that the gene produces its effect on development through the hormones as intermediaries

PARTHENOGENESIS

Parthenogenesis (*parthenos*, virgin, *genesis*, to be born) refers to the development of an individual from an unfertilized egg. The scientific literature contains no record of parthenogenesis in man, but among many groups of invertebrate animals, as well as in some plants, parthenogenetic development is the rule In a number of vertebrate animals, as we shall see below, parthenogenesis has been experimentally induced.

In some animals having natural parthenogenesis, e.g., in the group of insects known as plant lice, or aphids, the reduction division is omitted; consequently the unfertilized eggs have the double number of chromosomes and develop into females This is an illustration of *diploid* parthenogenesis In others, such as the honeybee, all of the eggs, including those that develop parthenogenetically, have undergone a reduction division, and the parthenogenetic eggs develop into males exclusively. These males have but a single set of chromosomes—an example of *haploid* parthenogenesis The sperms produced by these haploid males are formed without a reduction division and therefore contain the complete set of chromosomes It is an interesting fact, as Professor E B Wilson points out, that in the bee and many other hymenopterous insects

> a kind of vestigial reduction division takes place, the primary spermatocyte making an abortive attempt to divide, in the course of which an incomplete spindle is formed, and the chromosomes appear, but no nuclear division occurs. The result is the extrusion of a non-nucleated mass of protoplasm or "polar body," and this is followed by one complete mitosis in which both nucleus and protoplasm divide normally

It is probable that animals which now reproduce parthenogenetically are descended from ancient ancestors in which ordinary biparental reproduction was followed The ultimate step in this direction has been taken by a few species, such as the gallfly *Cynips kollari* and the praying mantid *Brunneria borealis* of our Southern states, among which males seem to

[1] O. N Eaton and V L. Simmons, Hermaphroditism in Milk Goats, *J Heredity*, 30:261–266, 1939

have become entirely unnecessary since they have never been found All the individuals are females and develop in each generation from unfertilized eggs

Obviously, no species are known in which males only and no females exist, for although the sperm is the equivalent of the egg so far as the genes are concerned, sperms are almost totally lacking in the cytoplasm and stored food which are necessary for embryonic development

The determination and differentiation of sex in species that reproduce parthenogenetically present highly interesting features The honeybee is



Figure 57. The honeybee, showing the three castes *Left to right* Queen, worker, drone. (*From Von Frisch, "Bees, Their Vision, Chemical Senses, and Language," Cornell University Press*)

a classic example. In a colony of honeybees there is one queen (a fully mature female whose function it is to lay the eggs), thousands of sterile females, aptly known as workers, and a few males, known as drones (Fig 57). Queens and workers are genetically alike both develop from fertilized eggs. Drones develop from unfertilized eggs.

Before she begins her duties of laying eggs, the queen goes on a nuptial flight, followed by a number of males The successful suitor mates with her high up in the air. For the realization of this function the male pays dearly, since a moment after mating, and as a result thereof, he dies The one supply of sperms received from the male is sufficient, however, to last the queen the rest of her life—which may be as long as four or five years, or in exceptional cases, longer.

Most of the eggs laid by the queen are fertilized by these retained sperms; such eggs develop into females A small number of eggs are not fertilized, and these develop into males Males thus possess no father, although they have had a grandfather.

The development of workers and queens is of unusual interest Since both come from fertilized eggs, which so far as known are exactly alike, the differentiation of worker and queen is due entirely to the environment. Their differences involve not only numerous structural details adapting each caste to its special work, but include instincts as well The queen is merely a queen mother she apparently has nothing to do with governing the colony, but devotes her whole energies to the laying of eggs and pays no attention to her own offspring after they hatch. The instincts of caring for the young, gathering food, and defending and maintaining the hive reside solely in the workers Only rarely are workers able to produce eggs

The workers alone control the development of a new queen in the following interesting manner An ordinary cell containing an egg or a larva under three days of age is first enlarged by the workers to allow room for the extra size of the queen-to-be During the first two days of life all larvae are fed "royal jelly," a white fluid secreted by glands in the mouth of worker bees. The larval queen continues to receive royal jelly during the remaining 2½ days of her larval existence. The larval workers are denied further royal jelly and after the first 2 days are fed on pollen and nectar only. They develop slowly and undergo pupation at about 8½ days, requiring about 18 days from egg to adult The queen requires a total of only 12 or 13 days for her development, and upon emergence is nearly twice the size of workers (Fig 57).

Artificial Parthenogenesis

Beginning with the brilliant discovery by Jacques Loeb in 1899 that eggs of sea urchins could be stimulated by chemicals to undergo parthenogenetic development, with the production of normal larvae, there has been a long list of similar successful experiments with various animals, including the vertebrates A great variety of chemical and physical agents have proved effective

In later experiments Loeb successfully raised frogs to sexual maturity from unfertilized eggs which had been treated merely by puncturing with a fine needle According to Wilson, in no other animals has it been possible thus far to rear larvae from artificially parthenogenetic eggs up to sexual maturity

Of the 20 parthenogenetic frogs brought through metamorphosis by Loeb, 15 were males, 3 females, and 2 of uncertain sex. The parthenogenetic frogs were found unexpectedly to have the normal diploid number of chromosomes, like frogs from fertilized eggs. Apparently there had been a doubling of the chromosome number in the unfertilized egg without cell division. The presence of both sexes in these experiments requires explana-

tion and calls for further experiments, with special attention given to the behavior of the chromosomes in the dividing cells

In mammals, fertilization normally takes place in the oviducts. If no sperms are present, the eggs pass on down the tubes, disintegrating in the lower end of the oviducts or in the uterus In a few cases in rats and rabbits, unfertilized eggs have been found in the tubes undergoing early cell division.[1] In such cases, however, the eggs soon die No instances of natural parthenogenetic development have been found in mammals

Dr Pincus, an investigator in this country, removed unfertilized eggs from the oviducts of rabbits and placed them in glass dishes containing blood plasma or serum He found that out of 213 eggs so cultured 136 underwent cell division, some as far as the 20-cell stage In some way the artificial environment stimulated the beginning of parthenogenetic development. Pincus suggests that the stimulus to cell division is an increase in the salt concentration of the culture medium through the loss of water by evaporation Such concentrated solutions are known to induce parthenogenesis in some of the lower animals After a time, however, usually under 36 hours in the culture medium, cell division ceased and the rabbit eggs disintegrated

Rabbit eggs have been successfully fertilized outside the body of the mother by the addition of a suspension of rabbit sperms to a culture dish containing the eggs. Under such circumstances development proceeds to a stage beyond that reached by parthenogenetic eggs Eventually, however, all such incubated eggs die The complete incubation of a mammal outside the body of the mother, a normal process in birds and the lower vertebrates, offers at present insuperable difficulties with respect to supplying nutriment to the embryo The successful imitation of the uterine environment is not, however, theoretically impossible That eggs fertilized outside the body are potentially able to continue development is proved by further experiments in which Pincus transplanted fertilized eggs into the oviducts of female rabbits The foster mothers that received these eggs produced from them normal litters, although such foster mothers had nothing to do with producing the eggs and had not mated with a male

PROBLEMS

1. Why did the earlier theories of sex determination often emphasize the environment rather than the nature of the reproductive cells?
2. Mention a chemical analogy to the mechanism of sex determination in grasshoppers, i e , name two chemical compounds with different qualitative properties, resulting from the presence of two atoms of some element in one compound and only one atom of the same element in the other compound

[1] Gregory Pincus, "The Eggs of Mammals," The Macmillan Company, New York, 1936

3. How is sex determined in the following: honeybee, grasshoppers, Drosophila, birds, mammals, plants?

4. Would you expect to find sex chromosomes in hermaphroditic species of plants and animals? If not, what may determine the differentiation of the male and female reproductive organs in hermaphroditic species?

5. List the advantages that hermaphroditic species may have over species with separate sexes. (In animals most hermaphroditic species are not self-fertilizing.)

6. What advantages have species with separate sexes over hermaphroditic species?

7. On the basis of what we have learned about the relation of gene to character, is it likely that the development of sexual characters depends upon one gene only or on several genes? Explain.

8. What are the various classes of evidence for the existence of identical twins in man?

9. What factors affect the frequency of two-egg twins in man?

10. Assuming an expected sex ratio of 1:1, what is the chance that of five offspring all will be males?

11. With a sex ratio of 1:1, what is the chance that the first three of five offspring will be males and the other two females?

12. With a sex ratio of 1:1, what is the chance that three will be males and two females, regardless of birth order?

10

SEX-LINKED HEREDITY

The solution of the problem of sex determination opened the way to the clearing up of another long-standing biological riddle For centuries people had been puzzled by the fact that certain hereditary characteristics appeared more frequently in males than in females, and yet the males in each generation seemed to inherit the particular characteristic through their mothers and not from their fathers The discovery of the chromosome mechanism of sex determination led directly to the explanation of this mystery.

COLOR BLINDNESS

Red-green color blindness in man is the commonest of the hereditary characteristics showing a peculiar relationship to sex. About 8 0 per cent of all white males show some lack of ability to distinguish between the colors red and green, while only about 0 5 per cent of white females are so affected. Such color-blind persons have normal vision with respect to black, white, yellow, and blue, reds and greens, however, in extreme cases of the defect, are not recognized as distinct colors, but are confused with yellows, blues, and gray

Color blindness varies in degree from a moderately weakened color sense for red and green to the complete absence of the sense Red-green color-blind persons commonly fail to distinguish between pale red, pale green, and gray, and at the same time are able to name correctly intense shades of these colors in a good light Consequently, in most cases it is better to speak of color weakness than of color blindness. The simplest and most widely used of the tests for color blindness yet devised are the color plates invented by Dr. Shinobu Ishihara, Professor of Ophthalmology, Imperial University of Tokyo

A rare type of hereditary total color blindness, accompanied by day blindness, or inability to see clearly in bright light, has also been described. To persons with this defect everything appears as black, white, or gray. According to many authors, it is inherited as an autosomal recessive Cousin marriages are relatively frequent among the parents of such defectives, this is evidence of recessive inheritance.

Yellow-blue blindness has occasionally been reported Its genetic basis is undetermined

Those of us who have normal color vision may get some idea of the world in which color-blind persons live by observing our own sensations during advancing twilight As the daylight diminishes in intensity, greens and reds first disappear, leaving yellows and blues still recognizable With deepening twilight, all colors vanish until everything takes on some shade of gray. The light from the moon is usually too weak to stimulate the color sense, consequently, we are all more or less color-blind by moonlight.

In all cases of congenital color blindness the cause seems to be hereditary, having nothing to do with age or training Tests of young children of both sexes have shown the same percentage of color blindness as in adults [1]

The physiological cause of color blindness is imperfectly understood, as, for that matter, is the physiology of color vision itself It is probably due to some defect of those specialized cells of the retina (the cones) which are concerned in color vision

In its mode of inheritance color blindness is sex-linked, i.e , its gene is located on the X chromosome. Heretofore we have spoken of the X chromosome as though it had nothing to do but determine sex. There is abundant evidence, however, that the X chromosome carries a miscellaneous assortment of genes, affecting various parts of the body, in addition to the gene or genes for sex determination The gene for color blindness, as well as the normal alternative gene, is one of these This statement is based upon a study of the pedigrees of color blindness rather than upon observations of the cells In the lower animals, however, particularly in Drosophila, sex-linked heredity of exactly the same type as in man has been shown by microscopical study to depend upon the presence of the X chromosome. The Y chromosome carries no corresponding gene, and this accounts for the difference in the percentage of color blindness in the two sexes

To illustrate how the mechanism of sex-linked heredity operates, let us consider the mating shown in Fig 58. Here the gene *c* for color blindness is found on both of the X chromosomes of the mother; she is, therefore, color-blind. The one X chromosome of the father in this mating carries the normal gene *C*; hence his vision is normal. The lack of either gene *C* or *c* on the Y chromosome is represented by a dash (-).

As shown in the diagram, the reduction division produces but one kind of egg as contrasted with the two kinds of sperms Fertilization results in the usual sex ratio of 1 male:1 female. All the daughters have normal vision, since they all receive the dominant gene *C* from their father. All

[1] R. W. Pickford, "Inherited Differences in Colour Vision," Routledge and Kegan Paul, Ltd., London, 1951.

the sons are color-blind, because their one X chromosome derived from their mother carries a gene for color blindness This result is known as crisscross inheritance, because the daughters resemble the father and the sons resemble the mother.

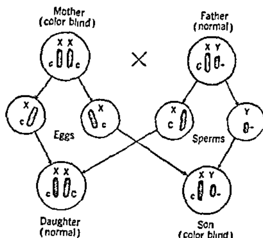
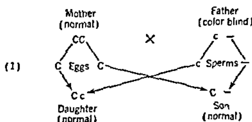


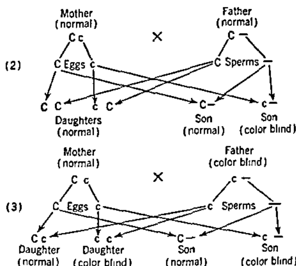
Figure 58. Diagram showing the inheritance of red-green color blindness in man, a typical case of sex-linked heredity

Whatever truth there may be in the popular belief that sons and daughters "take after" the parent of opposite sex rests entirely, so far as we know, upon this phenomenon of sex linkage The proportion of traits which are sex-linked in man cannot be very great because the X chromosome is only one of 24 in man (Fig 51), and it is one of the smaller ones, at that. If the genes are distributed equally among all 24 chromosomes, in proportion to the size of the chromosomes, less than 4 per cent of the genes should be found on the X chromosome In animals with a smaller number of chromosomes, the proportion of sex-linked genes is, of course, higher. Thus in *Drosophila melanogaster*, which has been studied more than any other animal, there are four pairs of chromosomes, and more than one-fourth of the known genes are sex-linked

Three other types of mixed matings involving color blindness are possible These are as follows

(1)





An inspection of the diagrams of the four possible mixed matings makes it clear why there are more color-blind males than females In three of the matings color-blind sons are produced, whereas in only one of the four are there color-blind daughters, this being the last mating shown, where the mother is heterozygous and the father is color-blind. Nearly all color-blind women must come from the last type of mating, since the only other possible source of color-blind females is matings between two color-blind persons—naturally a rare occurrence.

It is interesting to note that since 8 0 per cent of all males are color-blind there must be approximately twice that many women in the population who are carriers of the gene, for most color-blind males come from mothers who are carriers, and one-half of the sons of such carriers are, of course, color-blind.

Marriage between normal and color-blind persons is, no doubt, largely a random matter, color blindness being seldom, if ever, a deliberate factor in the choice of a mate Natural selection probably has had little effect upon the frequency of color blindness in the population, a fact which perhaps partially explains why color blindness is so common.

Socially important consequences of color blindness appear when we consider the large number of automobiles now in use and remember that 8 men in 100 are color-blind It is more than likely, under the circumstances, that not a few accidents are due to the misinterpretation of traffic signals Obviously, it is unfortunate that red and green were chosen as traffic-signal colors, yellow and blue would have been preferable, since nearly everyone can distinguish these colors. Railway, steamship, and air-transport companies, for years, have rejected color-blind applicants for certain positions, but very few states in this country have

rejected color-blind applicants for automobile licenses. Even under the existing system, greater safety undoubtedly would result from the practice of testing all drivers for color blindness and requiring those found to be color-blind to employ known methods of compensating for their deficiency.[1] Further changes in the quality of the colors in traffic lights to suit the needs of color-blind persons could be made

Interesting racial differences in the frequency of color blindness have been reported. Among white males the frequency (including all degrees of the defect) is about 8 0 per cent; among Chinese, about 6 5 per cent, among Negroes, about 4 0 per cent, and among American Indians somewhat less than for Negroes [2] The number of females tested in this country has not been large enough to give very reliable estimates, but in Oslo, Norway, Waaler tested over 9,000 schoolgirls and found 0.44 per cent to be color-blind. He also tested over 9,000 boys, finding 8 0 per cent color-blind

With 8.0 per cent of males color-blind there should be theoretically $(8.0)^2$ per cent, or 0.64 per cent, females color-blind—assuming that all color blindness is due to the same gene This calculation rests upon the fact that if matings are at random with respect to the gene and if there is no selection for or against it, the frequency of a sex-linked gene should be the same in both sexes The frequency of the gene in males is 8 per cent. Consequently 8 per cent of all genes at this locus in women should be *c*. This means that 8 per cent of all eggs will carry *c* With 8 per cent of eggs carrying the color-blind gene and with 8 per cent of X sperms also carrying *c*, a union of a *c* sperm with a *c* egg should occur in 8 per cent of 8 per cent, or 0 64 per cent, of female-producing fertilizations

Tests show that there are two qualitatively distinguishable types of red-green blindness. Some authors have designated these red blindness and green blindness, although in reality persons of both types are deficient in the red-green color sense If two different genes occupying separate loci on the X chromosome are responsible for the so-called red blindness and green blindness, as seems probable from the work of Waaler and later investigators (see Pickford, cited page 166), a female heterozygous for both of these genes will be normal, since she will possess the dominant alternative of each recessive gene. If the two genes happen to be on different chromosomes and if crossing over does not occur, all of her sons will receive either the one gene or the other; hence every son will be color-blind—half of them red-blind and half green-blind If the

[1] A method which makes use of red and green color filters attached to the windshield has been found effective with color-blind persons by Thomas Ross, of the University of Washington, who describes the method in detail in *Science*, 83:270, 1936

[2] Audrey M Shuey, The Incidence of Color Blindness among Jewish Males (and previous articles therein cited), *Science*, 84:228, 1936

red-blind gene and the green-blind gene are on the same chromosome, half of the sons should be both red-blind and green-blind and half should be normal, provided there is no crossing over.

In Fig 59 I have reproduced the pedigree of a woman student (II-7) from one of my college classes. This pedigree is of special interest because it can be interpreted most simply under the two-locus theory, with crossing over taking place in the maturation of certain ova. Letting the symbol *r* represent the red-blind gene and *g* the green-blind gene, the normal mother carries an *r* on one of her X chromosomes and a *g* on the

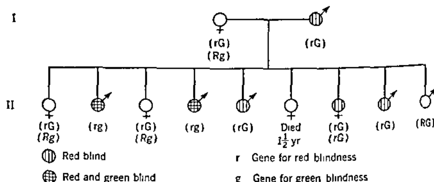


Figure 59. Pedigree of a family showing that five of the eight living children are color-blind The two-locus theory described in the text is applied to this pedigree.

other. Disregarding the female who died in infancy, there are under this hypothesis at least three crossovers among eight individuals, or 37.5 per cent. These are the two oldest sons, both (*rg*), and the youngest son (*RG*) The color-blind student, of course, may herself have received a crossover gamete (*rg*), in which event her genotype is (*rg*)(*rG*).

The pedigree diagram might just as well have been made to show the X chromosomes of the mother as (*RG*) and (*rg*), there *is no* way of telling from the characteristics of the offspring whether this *coupling* of the two recessive genes on one chromosome rather than the opposite arrangement (*repulsion*), *as shown in the diagram, is the correct* one If the two recessive genes in the mother are coupled, the two red-blind sons (II-5 and II-8) must be crossovers, making at least 25 per cent crossing over

Generation II in the pedigree is the kind of sibship that has been demanded as proof of the two-locus theory of color blindness [1] The pedigree does not fit the rival hypothesis, favored by a few authors, in which all types of red-green blindness are regarded as due to one series of mul-

[1] Gordon L. Walls and R W Mathews, New Means of Studying Color Blindness and Normal Foveal Vision, with Some Results and Their Genetical Implications, *Univ Calif. Publs Psychol*, 7:1-172, 1952

tiple alleles For under the single-locus theory there can be no crossing over, and all five sons should have been color-blind We see that one of them was normal.

The present weight of opinion among students of color blindness seems clearly in favor of the two-locus theory, with at least three alleles at each locus accounting for the variability in the expression of the trait The writer has found no other pedigree in the literature that seems to require crossing over as an explanation. Obviously, further studies of the problem are desirable

The normal allele is not always fully dominant over the gene for color blindness in women Heterozygous women may show some degree of red-green weakness The writer found two women students, sisters, who were color-weak, both missed several of the Ishihara plates Their father was completely green-blind as defined by Ishihara, their mother, mother's brother, and maternal grandfather and grandmother were all normal It is thus probable that they were heterozygous

OTHER SEX-LINKED CHARACTERISTICS IN MAN

Numerous other sex-linked characters are known in human beings, but none approaches red-green blindness in frequency Some are extremely rare. With very few exceptions they are recessive. Let us consider a few of the best-known examples.

Congenital Night Blindness with Myopia

Night blindness is in some respects the opposite of day blindness, which, as we have seen, is one manifestation of total color blindness In daylight, the night-blind person sees normally, but in dim light his vision is extremely defective The trouble seems to be with those cells of the retina known as the rods, which are specially adapted for vision in dim light Hereditary night blindness should not be confused with temporary night blindness, which is due to deficiency of vitamin A The sex-linked recessive form of night blindness is accompanied by nearsightedness (myopia).

There are two other types of hereditary night blindness, which are not sex-linked· one is an autosomal dominant and the other is an autosomal recessive. This is another illustration of the fact that similar phenotypes may be due to different genetic causes

Absence of Sweat Glands, Defective Teeth and Hair

Cockayne (see page 30) gives a good description of a striking hereditary condition which he calls "major ectodermal defect." His descrip-

tion, quoted in part below, is accompanied by references to numerous reported pedigrees

The main features of this rare and interesting developmental defect are small size and delicacy of constitution, a total absence or deficient number of teeth, conical incisors and bicuspids, and molars with sharp-hooked cusps, short, fine, pale, scanty hair, chronic rhinitis with subsequent loss of smell, absence of sweat glands, and sometimes, if not always, absence of the lachrymal glands

It has been reported among various peoples: English, German, Swedish, French, Russian, Jewish, and Hindus. It exists in the United States among peoples of various European descent.[1]

During hot weather the body temperature of persons without sweat glands tends to run up far above normal, resulting in considerable suffering Victims of the defect learn to avoid extreme discomfort by staying out of the sun and refraining from vigorous exercise and hot food and drink They also apply water to their clothing to gain the cooling effect *of evaporation A further heat loss is brought about by the automatic* speeding up of the rate of breathing, as in the case of panting dogs; dogs are not well supplied with sweat glands. Persons who have no sweat glands may be fairly active and comfortable during cool weather.

Hemophilia (Bleeder's Disease)

Owing to its presence in the royal families of Europe, hemophilia, or the "royal disease," is the most notorious of all sex-linked characteristics Its presence in royal families is, however, merely a coincidence, for it is no respecter of persons Like any other hereditary trait which gains admittance to a closely intermarrying group, hemophilia has come to have a supposed importance far beyond its real importance to the population as a whole

Hemophilia seems to have been described in detail first by John C Otto of Philadelphia in 1803[2] It is, nevertheless, one of man's ancient afflictions Albucasis, famous Arabian surgeon of the eleventh century, wrote of men in a certain village who bled to death from superficial wounds, and of boys who bled to death if their gums were rubbed harshly The ancient Hebrews evidently knew of hemophilia, for according to Dr. Birch, of the School of Medicine, University of Illinois, who has written a comprehensive illustrated monograph[3] on the subject, there

[1] E. Roberts, The Inheritance of Anhidrosis with Anadontia, *J. Am. Med. Assoc*, 93.277-279, 1929.

[2] J C Otto, An Account of an Hemorrhagic Disposition Existing in Certain Families, *Medical Repository*, vol 6, 1803

[3] Carroll La Fleur Birch, Hemophilia Clinical and Genetic Aspects, *Illinois Medical and Dental Monographs*, vol. 1, no 4, 1937.

are several undeniable references to hemophilia in the Talmud, *described* under dispensation from circumcision A similar reference is made by Dr. Aaron Friedenwald in "The Jewish Encyclopedia"

The primary symptom of the disease is an abnormal tendency to bleed because of an extremely slow rate of coagulation of the blood In normal individuals the blood from a ruptured vessel coagulates in from 2 to 8 minutes; in hemophiliacs the coagulation time is greatly prolonged, varying from ½ hour to 22 hours or more, according to the severity of the disease. In some families the disease is much more severe than in others.

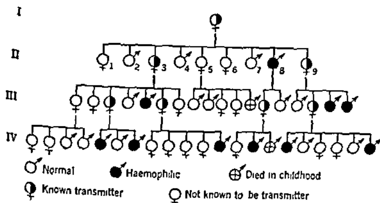


Figure 60. Pedigree of Queen Victoria of England, showing the distribution of hemophilia among her descendants *(Redrawn, with modifications, from Haldane.)*

The best-known pedigree of hemophilia is that of Queen Victoria of England (1819–1901), shown in part in Fig 60 The data were assembled by Haldane.[1] Victoria was heterozygous for the gene, perhaps owing to a new mutation; according to Haldane there is no record of hemophilia among her ancestors Numerous descendants of Victoria's normal sons and apparently homozygous daughters are not shown in the pedigree chart because of lack of space

Of Victoria's four sons, only one, Leopold, was affected He lived to be thirty-one, married, and passed the gene on to his daughter, who bore an affected son. This son, like his grandfather Leopold, died of hemophilia.

Victoria's first daughter, Victoria (II-1), was apparently free from the gene, since among her numerous children and grandchildren there was no hemophilia. Victoria's first son (II-2), who became Edward VII of England, was free from it.

Her daughter Alice (II-3) had an affected son, who died of hemophilia at the age of three, and two heterozygous daughters. The first of these

[1] J. B. S Haldane, "New Paths in Genetics," Harper & Brothers, New York, 1942.

(III-3) married Henry of Prussia, brother of Emperor William II of Germany, and bore two hemophilic sons and one normal son. Alice's other daughter, Alexandra (III-6), who became the wife of Tsar Nicholas II of Russia, was the mother of Alexis (IV-12), the last Tsarevitch, who suffered from severe hemophilia He and the other members of the royal family were shot by the Communists after the revolution, in 1918.

Victoria's other carrier daughter, Beatrice (II-9), bore a normal son, two hemophilic sons, and a daughter, Victoria Eugenie (III-16), who married Alfonso XIII, King of Spain. Two of Eugenie's four sons, including the Spanish Crown Prince Alfonso (IV-16), were bleeders; both died of the disease

Summarizing, it is evident from this pedigree that among Queen Victoria's descendants, ten males suffered from hemophilia, and all but two of these stem from two of Victoria's daughters; the other two were an affected son and his grandson Six female descendants of Victoria are known transmitters of the gene

It seems probable that the presence of hemophilia in the crown princes of the Russian and Spanish royal families may have had some influence in the overthrow of both dynasties, thus emphasizing the far-reaching effects of a single gene upon the destinies of families and of nations

Andreassen[1] studied all of the cases of hemophilia discoverable in Denmark He found 205 hemophilic males belonging to 63 families, consisting of 1,970 persons There were no hemophilic females The frequency of affected males at birth in the population of Denmark was estimated at 13 per 100,000

This absence of hemophilic females has been reported for various countries by many other investigators[2] How can we explain it? Since hemophilia is inherited as a sex-linked recessive, a female can develop the disease only if she receives the gene from her affected father as well as from her mother In view of the rarity of the gene in males (0 00013 in Denmark) and its theoretically equal rarity in females, plus the failure of most affected males to leave offspring, the production of a homozygous female from unrelated parents would occur with extreme rarity The lack of hemophilic females may thus be due to chance

Another theory accounting for the absence of hemophilia in females, suggested long ago and adopted by various authors, is that females who receive the gene from both parents die before birth The direct proof of such a lethal effect has not been obtained. Whether true in some cases or not, the theory does not apply universally. From Manchester, England,

[1] Mogens Andreassen, Haemofili i Danmark, *Opera ex Domo Biol. Hereditariae Humanae Univ Hafniensis*, 6:1-168, 1943 (reviewed in *Biol Abstr*, 22:766, 1948)

[2] Erik Sköld, "On Haemophilia in Sweden and Its Treatment by Blood Transfusion," P. A. Norstedt & Söner, Stockholm, 1944

comes a report of true hemophilia in a young woman[1] The father of the woman was a hemophiliac. Her mother had a hemophilic brother and thus could have been heterozygous for the gene Elaborate tests of the coagulating mechanism of the blood gave results characteristic of hemophilia in every instance. The woman's bleeding symptoms also were typical of hemophilia.

True hemophilia, expressed in both sexes and inherited as a sex-linked recessive, has been found in dogs.[2] Hemophilia is also known in hogs, but in hogs it is inherited as an autosomal recessive.

Sex-linked Lethals

By definition a *lethal gene* is a Mendelian factor that kills the individual. The time of action of the lethal gene may be anywhere from the gamete or zygote stage on through embryonic development and throughout the life of the organism On page 97 an autosomal recessive lethal gene was described, using the yellow mouse as an example In the mouse the lethal effect takes place very early in embryonic development In *Drosophila*, lethals are known in the zygote stage, as well as in the larval, pupal, and adult stages

Dominant lethal genes are also possible If such a gene kills before the individual reaches the reproductive stage, it obviously cannot be passed on to the next generation. Hence the gene could occur only as often as a new mutation arose. We would expect this to be a very rare event There is great difficulty in distinguishing a dominant lethal mutation from a very rare "accident of development" Probably some so-called accidents of development are results of dominant lethal mutations

Recessive lethal genes are common They may be autosomal, like the yellow mouse gene, or sex-linked In man the sex-linked gene for hemophilia is not far from being lethal in some families More often it is classed as semi- or sublethal, since a few hemophilic males do reproduce.

An interesting by-product of sex-linked lethals is their effect upon the sex ratio Rawls in 1912 first reported a change in the sex ratio in Drosophila that depended on a lethal In the same year Morgan[3] showed that the cause was a gene in the X chromosome He used Rawl's material. Rawls found one female that produced 222 daughters and 110 sons and another female that gave 308 daughters and 131 sons These ratios are close to 2:1. Something was evidently killing off about half of the sons

Morgan mated red-eyed females from Rawl's stock to white-eyed

[1] M. C. G Israëls, H Lempert, and Elizabeth Gilbertson, Haemophilia in the Female, *The Lancet*, 260:1375–1380, 1951

[2] K M. Brinkhous and J. B. Graham, Hemophilia in the Female Dog, *Science*, 111:723–724, 1950.

[3] T H. Morgan, C B Bridges, and A H. Sturtevant, The Genetics of Drosophila, *Bibliographia Genet.*, 2:1–262, 1925.

males (white eye is a sex-linked recessive) Some of the pairs gave an F_1 ratio of 2 females 1 male, as shown in the diagram below. The F_1 females were then backcrossed to white-eyed males; half of them produced a ratio of approximately 2 females 1 male, the other half gave normal ratios The three generations are diagramed below

MORGAN'S DEMONSTRATION OF A SEX-LINKED LETHAL IN DROSOPHILA
(w = white eye, l = sex-linked lethal)

P	Rawl's Red-eyed ♀ (*W L*)(*W l*)	×	White-eyed ♂ (*w L*)	
F_1's	2 Red-eyed ♀'s ½ (*W L*)(*w L*) ½ (*W l*)(*w L*)	.	1 Red-eyed ♂ ½ (*W L*)(live) ½ (*W l*) (die)	
Backcross F_1 ♀ × *w L* ♂	Red-eyed ♀ (*W l*)(*w L*)	×	White-eyed ♂ (*w L*)	
Offspring from backcross	Red-eyed ♀'s (*W l*)(*w L*) 448	Red-eyed ♂'s (*W L*) 2 (crossovers)	white-eyed ♀'s (*w L*)(*w L*) 452	white-eyed ♂'s (*w L*) 374

The two red-eyed males in the last generation were explained as crossovers. The opposite type of crossover (*w l*), which may have occurred, would of course have died and could not be observed Morgan pointed out that the results of this experiment could be explained by assuming that the female carried a lethal factor in one of her X chromosomes A further test of the theory was made All 448 red-eyed females in the last generation should be heterozygous for the lethal, hence they should give a 2 1 sex ratio regardless of the male to which they are mated. This was found to hold. The white-eyed females, however, should give a 1:1 sex ratio, which they did. The two crossover males should not pass on the lethal to their offspring; and this also was borne out Experiments with other mutant genes added to the evidence of a lethal gene near the locus of white eye on the X chromosome.

Returning for a moment to man, in the last chapter we saw that stillbirths are much more frequent in male embryos than in females, especially in the early stages It seems probable that some of this excess may be due to the presence of sex-linked lethal genes acting during embryonic life. Human males, like Drosophila males, have only one X chromosome; hence there is no normal allele to counteract the effect of a sex-linked lethal gene.

Y-CHROMOSOME INHERITANCE

The Y chromosome (Fig. 51) does not carry genes for ordinary sex-linked characteristics such as those just considered, but pedigrees have

been published for a few characteristics which strongly indicate that their genes are located on the Y chromosome. In such cases the X chromosome carries no corresponding gene. One of these Y chromosome traits is a remarkable type of scaly skin (ichthyosis hystrix gravior), first described more than a century ago in England Cockayne gives a good account of the characteristic with a review of the literature relating to it The defect first appeared in the son of a country laborer named Lambert, and the boy was shown before the Royal Society in 1731 A description written by Machin in 1732 follows.

> The skin seemed rather like a dusky coloured thick case, fitting every part of his body, made of rugged bark, or hide, with bristles in some places, which case covering the whole of him excepting the face, the palms of the hands, and the soles of the feet, causing an appearance as if those parts alone were naked, and the rest cloathed . . It is said he shed it about once a year, about autumn, at which time it usually grows to the thickness of three-quarters of an inch, and then is thrust off by the new skin which is coming up underneath The bristly parts, which were chiefly about the belly and flanks, looked and rustled like the bristles, or quills, of an hedge-hog, shorn off within an inch of the skin his skin was clear at birth as in other children, and so it continued for about seven or eight weeks, after which, without his being sick, it began to turn yellow, as if he had had the jaundice, from which by degrees it changed black, and in a little time afterwards thickened, and grew into the state it appeared in at present.

Both parents of this boy were normal, which indicates that a new mutation had occurred The condition was passed on for five generations, and affected individuals were studied by some of the leading scientific men of the day. A number of articles were published describing members of later generations; all these reports agree with Machin's description In each case it was emphasized that all affected individuals were males and that affected men transmitted the condition to all of their sons and to none of their daughters, their daughters never transmitted it to any of their children of either sex A pedigree of the family drawn up by Cockayne is shown in Fig 61. An inspection of this interesting pedigree shows that the characteristic is distributed exactly as it should be if the gene is located on the Y chromosome Cockayne states that there were more children of both sexes in the later generations than he has indicated

Webbed toes (fusion of the flesh and skin between the second and third toes) is another characteristic which is inherited in exactly the same way as the one just described. The evidence is based upon a pedigree of his own family published by Schofield,[1] in which four generations are shown. The pedigree represents 14 affected males and no affected females Every father transmitted the condition to all of his sons but to none of his daughters. (See pedigree, page 180) Reports have been published of

[1] R. Schofield, Inheritance of Webbed Toes, *J. Heredity*, November, 1921.

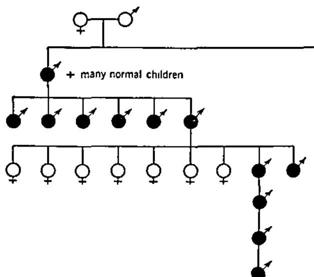


Figure 61. Pedigree of the Lambert family showing Y-chromosome inheritance of ichthyosis (*After Cockayne*)

several other traits which follow the Y-chromosome type of inheritance Among these are hairy ears (hypertrichosis).

PROBLEMS

In Drosophila, the normal wing (*VV*) is an ordinary dominant over vestigial wing (*vv*) White eye (*ww*) is a sex-linked recessive, the normal red eye (*WW*) is dominant

1. Indicate the eye color and the genotypes of the parents in the three matings which produced the following results·

	Red-eyed ♀'s	White-eyed ♀'s	Red-eyed ♂'s	White-eyed ♂'s
(*a*)	93	0	45	55
(*b*)	100	0	0	95
(*c*)	50	45	46	40

2. Show the visible ratio among the offspring of a cross between a female heterozygous for both vestigial wing and white eye, with a white-eyed male heterozygous for vestigial. (In all problems involving sex linkage the ratio for each sex must be indicated separately.)

3. Show the results of a cross between a white-eyed vestigial female and a red-eyed heterozygous normal-winged male.

4. Indicate the phenotype and the genotype of each parent in the matings which produced the following offspring:

	Females				Males			
	Red normal	Red vestigial	White normal	White vestigial	Red normal	Red vestigial	White normal	White vestigial
(a)	90	85	98	80	97	90	95	80
(b)	140	135	0	0	0	0	145	130
(c)	48	15	43	14	50	15	45	12

5. In birds the female is heterogametic for sex ♀, XO, ♂, XX *Barring* of the feathers is a sex-linked character in chickens The gene for barring (*B*) prevents the formation of pigment at intervals along the length of the feather, resulting in alternate white and dark bars Gene *B* is incompletely dominant *BB* causes light barring, with relatively wide white bands, a single dose of the gene (*Bb* in males and *B* in females) produces dark barring, with narrow white bands, *bb* and *b* give solid-colored feathers.

Calculate the expected phenotypic ratios in the following matings

a. Light-barred male × solid female
b. Dark-barred male × solid female
c Dark-barred male × barred female
d. Solid male × barred female

6 In cats, as in other mammals, the male is heterogametic for sex The gene for yellow (*y*) is sex-linked: *y* males are yellow, *Y* males are nonyellow, *yy* females are yellow, *Yy* females are "tortoise shell," a mixture of yellow and some other color such as black; and *YY* females are nonyellow

Calculate the expected phenotypic ratios in the following matings (indicating all nonyellows as black).

a. Tortoise-shell female × black male
b. Tortoise-shell female × yellow male
c. Black female × yellow male.
d. Yellow female × black male.

7. In the following problems assume that color blindness is present in 0 64 per cent of the women and in 8 0 per cent of the men in the entire population and that marriages are purely at random so far as this character is concerned.

Calculate the percentage of marriages in which

a Both the man and the woman are color-blind
b Neither the man nor the woman is color-blind
c. The man is color-blind and the woman is normal
d The woman is color-blind and the man is normal

8 Assume that the frequency of hemophilia in a population is 0 00013 and that there are no affected females, but that 0 00026 of the females are heterozygous for the gene Also assume that no affected males marry

Calculate the frequency of hemophilia in each of the next two generations, disregarding the occurrence of new mutations

9. A woman whose maternal grandfather suffered from hemophilia has parents that are normal The woman's husband is normal What is the chance that her son will be normal? What is the chance that her daughter will be normal?

10. A woman whose maternal grandmother was a carrier of the gene for hemophilia and whose maternal grandfather was normal has parents that are normal What is the chance that her son will be hemophilic? What is the chance that her daughter will be a carrier?

11. A certain recessive lethal gene l in man is carried on the X chromosome but not on the Y chromosome. An individual who fails to receive at least one dose of the dominant allele L dies before birth In a mating between a normal male and a heterozygous female show the expected sex ratio of living births

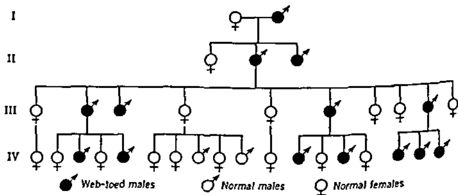
12. Construct a pedigree showing how a gene for hemophilia carried by a normal great-grandmother may be transmitted through grandmother and mother to a boy, making its presence known only in this, the fourth, generation. Assume that all male ancestors of the boy are normal Indicate the genotype of each ancestor of the boy in the direct line from his great-grandmother.

13. A boy has a great-great-grandmother on his mother's side who is known to be a carrier of the gene for hemophilia His mother traces back to this ancestor through the female line alone No other evidence of hemophilia has appeared among the ancestors of the boy What is the chance that the boy inherited the gene for hemophilia?

14 Assume that all hemophilic females who are homozygous for the hemophilia gene die before birth and that in one male birth in 50,000 the child receives a gene for hemophilia from his mother. If none of these genes is the result of a new mutation, what is the proportion of mothers who are carriers?

15 Explain the fact that most of the sex-linked characteristics so far discovered in man are recessive, whereas among Mendelian characteristics that are not sex-linked the majority so far discovered are dominant

16. In Schofield's pedigree of webbed toes, shown below, if you assume that the gene for webbed toes is an ordinary non-sex-linked dominant and that the male in generation I is heterozygous for the gene, what is the probability of obtaining such a run of webbed toes in males only and normal toes in all females as shown here? (Assume that all parents not shown in the pedigree are normal) *Hint:* The affected males produced by affected males and the normal females from affected males may be considered as two independent runs and their probabilities of occurrence calculated The probability of the two runs occurring simultaneously may then be obtained.



Pedigree of the Schofield family indicating Y-chromosome inheritance

17. If we assume that the gene for hemophilia is present in Europeans with a frequency of 0 00013 and if we further assume that hemophilic males produce on an average only 30 per cent as many children as normal males, what is the chance that a hemophilic female will be produced? Assume that there is no marriage between relatives and no assortative mating with respect to the gene for hemophilia

11

HEREDITY AND ENVIRONMENT

Not so long ago, when much less was known than we know today about the relative importance of heredity and environment in the development of the individual, a favorite topic for debate ran somewhat as follows: "Resolved that heredity is more important than environment," or "Resolved that environment is more important than heredity." The debater usually held strong convictions one way or the other upon the subject, and what he necessarily lacked in valid evidence to support his thesis, he abundantly made up for in emotional fervor

Today, considering the contribution of modern investigations in the field of genetics, all serious students of the subject realize that the question as stated above is not debatable We now know that both heredity and environment are indispensable in the life of every organism; and if both are indispensable, neither can be considered more important than the other. In fact, the question becomes debatable only when it is limited to a single characteristic of individuals within a specified population and subject to a given environment for example, "Resolved that heredity is more important than environment in determining the difference in height (or weight, or IQ) among individuals living under the ordinary conditions found in the United States"

Let us now consider some of the facts which make necessary such limitations of the subject.

GENES INHERITED RATHER THAN CHARACTERISTICS

In the period immediately following the rediscovery of Mendel's work the role of heredity in the development of the organism was often overemphasized Characteristics were looked upon as units and were thought to pass from parent to offspring with little regard to the environment Further investigation soon showed the incompleteness of these ideas. As we have seen already, the discovery of the factor principle proved that the gene rather than the characteristic was the unit of heredity; and when, in turn, attention was directed to the role of environment, it was recognized that the genes themselves were merely factors in develop-

ment Genes, we are now aware, can do nothing by themselves; genes can work only in cooperation with the environment.

Let us now examine a few clear-cut examples of the effect of the environment on plants, on animals, and on man, afterward we shall consider a number of more complex cases in man—some of which are of the greatest importance to human welfare.

LIGHT AS A FACTOR IN PLANTS

In Indian corn we have an excellent example of the rule that "what a gene can do the environment also can do" Although this rule is perhaps



Figure 62. Albino corn seedlings growing among normal green plants A similar population is growing under the box in the absence of light.

seldom literally true, it is a fact that a change in the environment often produces an effect that is very similar to a gene effect To illustrate, a recessive lethal mutation known as albinism prevents the development of chlorophyll in the corn plant. A large number of mutant genes in at least four different chromosomes have this effect. Seeds that receive a double dose of one of these albino genes sprout normally, and the young albino seedlings grow rapidly for a time, using the food stored in the seed When their food is exhausted, after they have reached a height of 10 or 12 inches, they die of starvation. Among their green neighbors the albinos present a striking color contrast, being almost pure white (Fig. 62). If normal seeds and albino seeds are planted together in a tray, which is then covered to exclude all light, all of the plants, normal as well as albino, will grow up without chlorophyll. At a little distance all look alike (Fig.

63), although on close examination the normal plants, unlike the albinos, have a slightly yellowish tint Lack of light has thus duplicated the effect of the recessive gene in preventing the development of chlorophyll

If the plants are kept covered until the food stored in the seeds is exhausted, all of the plants living in the dark will die, for the same reason that the albino plants die even in the light, namely, inability to manufacture food. If, however, the genetic green plants that have lived in the dark are exposed to the light in time, a good recovery will be made.

This experiment clearly demonstrates that light is just as necessary as the right genes for the normal development of green plants

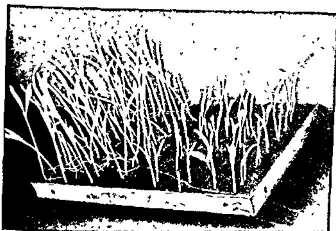


Figure 63. Corn seedlings, all of the same age. The tall white plants at the left grew in the dark.

In order to make the above-described demonstration a controlled experiment all environmental factors save the one which is to be varied should of course be held constant. Although the apparatus does not fully meet this ideal, it is probable, considering the known facts of plant growth, that the chief effective factor in the observed differences is light. The cover shown in Fig. 62 is an open box of galvanized iron The central region of the top is perforated in order to permit circulation of air into and out of the cover. A second iron top is fastened inside the box about one inch below the outer top This inner top is about one inch smaller in both dimensions than the box, thus allowing circulation of air without the admission of light to the plants As a further precaution all inside surfaces are painted black for the absorption of reflected light rays entering through the holes in the top

The apparatus as described probably furnishes a reasonably good control of all factors in the environment except humidity. Under the box the humidity is naturally much higher than it is outside. Differences in con-

centration of carbon dioxide and oxygen and temperature differences are probably insignificant if the box is kept out of the direct rays of the sun

In Fig. 63 other interesting environmental effects may be noted: the corn grown in the dark is much taller than that raised in the light; also, some of the roots of the dark-treated plants are growing aboveground

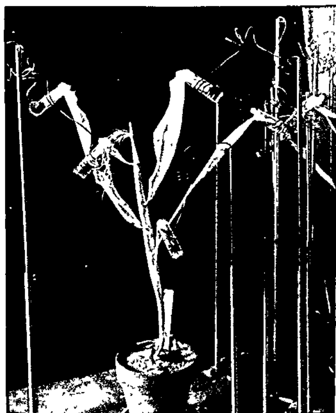


Figure 64. Albino maize plant, in sand culture, grown with 0 3 molar sucrose solution as only organic nutrient, fed through the leaves (*From Spoehr, Plant Physiology*, **17**:400, 1942.)

Although the albino gene is lethal under ordinary conditions, experiments have shown that the albinos are not irrevocably doomed to die of starvation. By feeding the albino plants sugar (sucrose) through the leaves, Spoehr[1] was able to extend their lives to four months and to bring them to the flowering stage Some of his plants produced both staminate and pistillate flowers and the same number of leaves as normal green plants (Fig 64) He kept some of the albinos in the dark, and these reached a height of 80 to 100 cm and bore rudimentary ears Some

[1] H. A. Spoehr, The Culture of Albino Maize, *Plant Physiol*, **17**:397–410, 1942

of the plants produced pollen, but Spoehr does not mention any functional seeds having been produced by the albinos

ULTRAVIOLET RAYS AS A FACTOR IN MAN

A familiar example of the effect of radiation simulating gene action in human beings is "tanning" of the skin In the process of tanning, ultraviolet rays stimulate the development of pigment in the skin, provided there are present also the proper genes for tanning Some persons (albinos and certain types of blondes) are unable to tan under any conditions Brunettes, in general, tan more readily than blondes

Since the color of the human skin depends upon genes, as well as upon the environment, it is obvious that we cannot always tell by looking at two persons whether their differences in color are due primarily to genes or to the environment The circumstances surrounding each case must be known.

Another instance of the effect of ultraviolet rays on genetically different members of our species has to do with the deficiency disease known as rickets This disease is characterized by imperfect development of the bones and teeth Rickets was formerly common among babies and young children in northern cities, where ultraviolet rays from the sun are largely excluded by smoke, fog, and clouds for many months of the year It is said to be extremely rare in the tropics, for exposure to the sun's rays causes the human skin to manufacture its own vitamin D, which prevents rickets.

There is good evidence, however, that heredity also is an important factor in the development of rickets This has been shown by the study of children within the same family, where frequently some of the children develop the disease while others remain healthy. Several studies made in Germany indicate clearly that there are hereditary differences in susceptibility to rickets. Stern[1] cites figures from such a study concerned with rickets in twins Among 60 pairs of identical twins there were 53 pairs in which both twins had rickets. In marked contrast, there were only 16 pairs of fraternal twins among 74 pairs in which both members were affected The environment was probably about as uniform for the fraternal twins as for the identical twins. However, the fact that there were seven pairs of identical twins showing lack of concordance with respect to the disease shows that heredity is not the sole factor.

Cancer of the skin in man is another pathological characteristic in which both heredity and environment play parts. Exposure of the skin to intense sunlight over a period of many years is a factor in the induc-

[1] Curt Stern, "Principles of Human Genetics," W. H Freeman and Co, San Francisco, 1949

tion of cancer of the skin in whites It has little or no effect in Negroes Comparisons between whites and nonwhites in three American cities in which there is a considerable difference in annual hours of sunlight is instructive (Table 14).

TABLE 14 SKIN CANCER INCIDENCE PER 100,000 POPULATION*

City	Year	Total hours sunshine	Whites		Nonwhites	
			Males	Females	Males	Females
Chicago	1947	2,560	26 2	22 7	3 6	4 3
New Orleans	1947	2,732	108 0	67 3	4 0	8 4
Dallas	1948	3,201	138 2	82 5	5 3	4 8

* *U S Public Health Service Cancer Morbidity Series*, New Orleans, No. 3, 1951; Chicago, No 6, 1952, Dallas, No 7, 1952

There is little difference among the three cities in the liability of nonwhites to skin cancer In contrast to this there are great differences among the cities in rate of skin cancer in the whites. In Dallas and New Orleans the white males show much higher frequencies of skin cancer than do females, probably related to greater exposure of the males to sunlight; in Chicago the sexual difference is not great, but it is in the same direction

It is obvious that there is a positive correlation between the total hours of sunshine and the frequency of skin cancer in the three cities But the rather small difference of 6 7 per cent hours sunlight between Chicago and New Orleans cannot alone account for the great difference of 312.2 per cent in the frequency of skin cancer among males in the two cities The important factor is of course the quantity of ultraviolet radiation absorbed by the human skin. As pointed out by R. E. Lautzenhiser, climatologist of the U S Weather Bureau in Chicago, who furnished the data on sunshine in Table 14, sunshine hours alone cannot be used as an accurate measure of total ultraviolet radiation received, since latitude affecting angle of incidence and differences in moisture content of the atmosphere are important variables. Differences in the amount of smoke and dust in the air are also probably very important, as are differences in temperature in the three cities. The temperature in Chicago is low enough for seven or eight months of the year to deter most persons from any protracted exposure of the skin to the sun. Unfortunately, data on ultraviolet radiation reaching the earth in the three cities seem not to be available

Experiments with mice and rats have shown that the cancer-inducing rays are of the same wavelength as those that cause sunburn. Such radiations are especially dangerous to persons with light-colored eyes, who

usually have fair skins, and many of whom never tan, this correlation between skin cancer and complexion was shown in a study of 100 consecutive cases of skin carcinoma in Los Angeles, by Hall[1] Of the 100 cases, 87 per cent were light-eyed, while among a comparable control group of patients other than skin-cancer patients only 53 per cent were light-eyed.

TEMPERATURE AS A FACTOR

In plants numerous cases are known in which the effect of a change in temperature may resemble closely the effect of a change in a gene In the Chinese primrose (*Primula sinensis*) there is one variety which produces red flowers at 20°C., but white flowers at 30°C or above By moving the plant from one temperature to another both red and white flowers may be obtained on a single plant Another variety develops white flowers at both temperatures.

In animals a similar relationship between temperature and gene is shown beautifully in a breed of domesticated rabbits known as the Himalayan. Under ordinary temperature conditions these animals have a conspicuous color pattern. The skin and fur are white except on the feet, ears, nose, and tail, which are black. The eyes are pink. This pattern is a single recessive with respect to the wild color

A simple experiment serves to show, however, that pigment formation on the extremities, without pigment formation on the rest of the body, depends upon temperature differences in the skin. If a patch of hair is plucked from the back of an adult animal and the rabbit is then placed in a cold room, the new hair coming in will be black After the spot has become covered with new hair, and thus protected from the cold, any new hairs that appear later will be white And as new hairs replace those lost by shedding, the dark spot gradually disappears

Conversely, if hair is removed from one of the pigmented extremities and the bare spot protected with a bandage, thus raising the temperature of the skin, the new hairs that grow out will be white

If the newborn animals are placed in a temperature as low as 11°C for only a few minutes and then returned to a warm room, the hair as it appears will be pigmented over the entire body It has been found that the short exposure to cold induces the formation of an enzyme in the skin which is necessary for the formation of pigment Once the enzyme is formed it continues to function even at high temperatures Normally, pigment is not formed in these rabbits at temperatures above 33°C.

It is obvious from these results that the Himalayan color pattern as such is not inherited. What is inherited is the gene which permits the

[1] A. F. Hall, Relationships of Sunlight, Complexion and Heredity to Skin Carcinogenesis, *Arch. Dermatol and Syphilis*, 61:589–610, 1950

development of pigment at temperatures up to a certain maximum; beyond this maximum the gene prevents the development of pigment

The color pattern of the Siamese cat (Fig. 65) and of the albino guinea pig is subject to a temperature effect similar to that of the Himalayan rabbit The guinea pig, however, develops much less pigment than the other two animals

Although we know of relatively few cases in which genes are as nicely balanced with the environment as those just considered, the principle



Figure 65. Siamese cat, a color variety corresponding to the Himalayan rabbit and the albino guinea pig Pigment develops on the extremities as a result of temperatures lower than on the rest of the body. *(From Thompson et al, J. Heredity,* April, 1943, p 122)

illustrated undoubtedly applies to most genes. A series of examples could be given, beginning with those in which a change in the environment anywhere within the range tolerated by the organism, produces no obvious effect on the characteristic, e g , eye color, and ending with those in which, like the Himalayan rabbit, a moderate change in the environment produces a marked effect Experience alone can tell us to what extent a given characteristic may be modified by the environment.

HORMONES AS A FACTOR, BALDNESS

There are several environmental factors that may cause loss of hair (baldness) in man among these are infections and hormones. Baldness is much more frequent, as well as more extreme in manifestation, in men than in women; the differences between the sexes are, of course, primarily hereditary.

Aristotle, in his zoological work *Historia animalium,* states that neither castrated men nor women ever grow bald. With certain qualifications, mentioned below, this statement is true.

Dr. James B. Hamilton,[1,2] of State University Medical Center in New York City, has made extensive studies of baldness in both sexes and in persons of all ages. His definitions of baldness of various degrees and types are shown graphically in Fig 66. The drawings show the typical

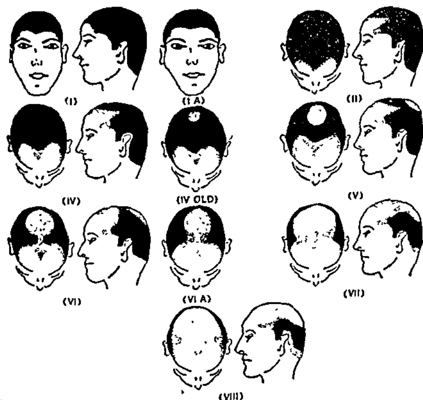


Figure 66. Sketches of the types of scalp hairiness used in the classification and grading of the extent of common baldness. Types I and II do not qualify as baldness. Types IV, V, VI, VII, and VIII represent a graded progression of common baldness. (*From Hamilton, Ann N.Y. Acad Sci*, 53:712, 1951.)

sequence of loss of hair in Caucasians, Negroes were not studied The stage at which loss of hair constitutes baldness (type IV) was arbitrarily fixed to include deep frontotemporal recessions, usually symmetrical, that are either bare or very sparsely covered with hair. Also, there is usually

[1] J. B Hamilton, Male Hormone Stimulation Is Prerequisite and an Incitant in Common Baldness, *Am J. Anat*, 71:451–480, 1942.

[2] J. B. Hamilton, Patterned Loss of Hair in Man: Types and Incidence, *Annals N.Y. Acad Sci*, 53:708–728, 1951

some loss of hair along the midfrontal border of the scalp. In old persons, especially men, the minimum loss of hair that qualifies as baldness may occur on the crown (see diagrams).

The frequencies of baldness, as thus defined, are shown in Fig 67. Since baldness makes its appearance at various ages and is progressive in degree, the extreme types are naturally more numerous at advanced ages In none of the 214 women studied by Hamilton was baldness more

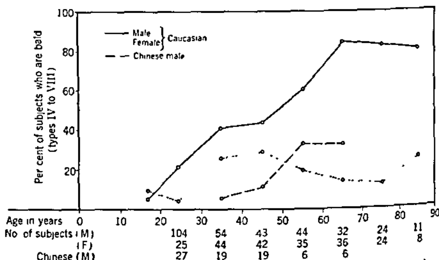


Figure 67. The incidence of common baldness of types IV to VIII in Caucasian males and females and in Chinese males (*From Hamilton, Ann. N Y. Acad Sci*, 53:720, 1951)

advanced than stage IV, although 58 per cent of the 112 men over 50 years of age showed baldness of types V to VIII.

Hamilton's investigations confirm the theory that baldness depends first upon an inherited tendency (a dominant gene, according to some authors[1]) as well as upon a certain concentration of male hormones in the blood He found no records of boys castrated before puberty who had become bald Nor did baldness develop in men who failed to mature sexually; but when these men were treated with male hormones loss of hair took place in men whose pedigrees showed them to be genetically susceptible to baldness Men who were castrated after becoming bald did not regain their hair, but no further loss of hair occurred. Sexually mature men, whether bald or with normal hair, did not differ significantly in concentration of male hormones

[1] H. Harris, The Inheritance of Premature Baldness in Men, *Ann. Eugenics*, 13:172-181, 1946.

PRESSURE AS A FACTOR

Deformation of the skull has been widely practiced by many tribes in Africa, Asia, and the Americas In infancy, while the bones are incompletely formed, continuous pressure is applied in one way or another. The Mangbetu, a Sudanese tribe in the northeast corner of the Belgian Congo,



Figure 68 Environmental modification of the skulls of children of the Mangbetu tribe, Belgian Congo Boy, *left*, girl, *right* The ear lobes show hereditary differences: free lobe, *left;* attached lobe, *right* (*Courtesy of Belgian Government Information Center, New York.*)

are an interesting example The head is bound, to produce an extreme elongation of the skull, as shown in Fig 68 There is no evidence that deformations such as this have any hereditary effect In some cases the practices suggest a desire to exaggerate a trait already somewhat characteristic of the population.

FOOD AS A FACTOR

In our study of Mendel's experiments with peas we learned that genes may have striking effects on size and growth. A single gene difference may account for the difference between a normal individual and a dwarf in

peas, in mice, or in men Similar striking effects may be produced by altering the food intake Both in plants and animals dwarfs can be produced at will by depriving the growing young of adequate food

Since genes as well as food affect the normal growth of organisms, it is often difficult to tell how much of the difference in stature among human beings is due to genes and how much to the environment; this is especially true of the young Measurements of school children in various countries have shown that the stature of children at given ages has increased during the past few generations For example, Professor Otto L. Mohr, of the University of Oslo, Norway, gives figures on the height and weight of students in the public schools of Oslo for the year 1920 compared with 1930[1] The portion of his table relating to height is shown in Table 15

TABLE 15 TEN-YEAR INCREASE IN HEIGHT IN SCHOOL CHILDREN, OSLO, NORWAY*

Above the double line, pupils in lower public schools. Below the double line, pupils in higher public schools (grammar school, gymnasium)

Age, yr	Sex	Body height, cm.		
		1920	1930	Increase
10	Boys	130 91	135 13	4 22
	Girls	130 02	134 59	4 57
14	Boys	148 22	153 10	4 88
	Girls	150 60	154 94	4 34
14	Boys	153 46	157 39	3 93
	Girls	154 91	158 52	3 61
18	Boys	173 55	176 07	2 52
	Girls	161 64	164 69	3 05

* From Mohr

Increases in weight were similar to those in height. Mohr states that in Norway all schools, both lower and higher, are public schools and that his figures are from the very complete statistics collected by the municipal-school physicians

His explanation of this remarkable increase over the ten-year period is as follows:

> As seen from this table there is a most remarkable general increase of stature and body weight in the course of the last ten year period It is perfectly clear that the genotypical quality of the population cannot have changed perceptibly during so short a time The very striking change must be due to the improvement

[1] Otto L. Mohr, "Heredity and Disease," W. W. Norton & Company, Inc , New York, 1934.

of environmental conditions, better hygiene, better nourishment etc The experts in their comments upon this evidence point particularly to the fact that the widespread application of birth control has reduced the size of the family very considerably. The number of births in Oslo was 4,900 in 1920, 2,100 in 1933 It is a matter of course that in small families each child will have much better care, i e, much better environmental conditions, than will be the case in large families with correspondingly limited financial opportunities

A question might be raised as to whether the explanation is necessarily as simple as Mohr indicates. To rule out completely genetic changes it seems necessary to show that the fall in birth rate was as great among tall members of the population as among short If the fall in birth rate was less among genetically tall people, the net result of such selection would be a rise in average height of children

A second genetic factor tending to increase stature in a heterogeneous population is the marriage of unlike types, resulting in what is known as hybrid vigor (Chap. 13).

Whether or not either of these factors has any force in the Oslo situation is not discussed, but in American cities it would seem unsafe to rule them out entirely.

Assuming that the differences shown in the table are largely environmental, we must remember that an increase in the stature of children of various ages due to improvement in the diet and other hygienic conditions does not ordinarily mean an increase in the adult stature

Studies of the height of London school children over the past 45 years have shown a gain of several inches in stature There has, however, been no demonstrable change in the adult stature During the past century the height of adult men has remained at about 67½ inches What has happened is an acceleration in the rate of growth[1] The age at which maximum growth was reached fell from about 26 years in 1880 to 21½ years in 1945. Mohr's table suggests a speeding up of the rate of growth in the earlier years

Numerous experiments with animals have shown that diets deficient in certain respects may cause a temporary retardation of growth, but that when the diet is corrected, growth will begin again, and may continue even beyond the age at which it would normally cease. Growth may even continue until normal size is reached. On the other hand, if the diet is deficient in vitamin D and minerals necessary for bone formation, a permanent stunting and malformation may result.

From the preceding discussion it is evident that the solution of problems of the relative force of heredity and environment requires controlled experiments Experimenting with man is out of the question, but

[1] G M. Morant, A Discussion on the Measurement of Growth and Form, *Proc. Roy. Soc. (London)*, B,137:443, 1950

fortunately nature herself has done a controlled experiment for us in the production of human twins The study of twins provides some of the best evidence we have on the relative importance of heredity and environment in man

IDENTICAL TWINS AND FRATERNAL TWINS

The origin of identical twins and fraternal twins has already been discussed in some detail (Chap 9) Briefly, we found that identical twins come from a single fertilized egg and therefore have identical sets of genes, whereas fraternal twins come from separate fertilized eggs and therefore are no more alike genetically than if they had been born at different times

The environment of a pair of twins of the same sex reared in the same family is about as uniform as can be found for human beings, hence most of the differences between them, which in the case of fraternal twins are often great, must be due to gene differences

Assuming that the environment is equally uniform for identical and same-sexed fraternal twins, a comparison of the two types tells us much about the role of heredity in human development. Characteristics which are usually present in both members of a pair of identical twins, if present in either one, but which are usually not present in both members of a pair of fraternal twins, must have a strong hereditary basis. Such characteristics are naturally relatively rare in the population as a whole Nevertheless, there are many examples of rare hereditary defects and diseases affecting both members of a pair of identical twins Some of these are mentioned in later chapters on human heredity.

The comparison of the two types of twins as a means of detecting hereditary traits has been widely used in Germany, and to a considerable extent more recently in the United States The method has been applied to all sorts of physical and mental characteristics, including the study of criminal behavior

Since 1928 four books have been published in Germany reporting studies on crime in twins.[1] The writers of all four books found from their investigation among prisoners that a criminal career in an identical twin was far more likely to be matched by a criminal career in his twin partner than is the case under the same circumstances with fraternal twins Combining the numbers from all four studies, one obtains 66 pairs of identical twins in 45 cases both twins were convicted of crime; in 21 cases only one was convicted There were 84 pairs of same-sexed fraternal twins: in 32 cases both twins were convicted of crime; in 52 only one was

[1] One of these books, "Crime and Destiny," by Johannes Lange, has been translated into English by Charlotte Haldane, published by Charles Boni, New York, 1928 For a review of the four books see P Popenoe, Twins and Criminals, *J Heredity*, October, 1936

convicted. In this country similar studies were made by Rosanoff and his associates[1] The results are similar to those from Germany Among 37 pairs of identical twins both were convicted of crime in 25 cases, in 12 pairs only one was convicted Among 28 pairs of same-sexed fraternal twins both were convicted in only 5 instances, in 23 cases only one was convicted.

In twin studies there is said to be *concordance* when both members of the pair are alike in the characteristic under study In all five studies combined there was concordance in 68 per cent of identical twins as contrasted with only 33 per cent among the fraternal twins If the percentage of concordance in the fraternal twins seems high, it should be remembered that these twins also have many genes in common, received from their common parents, which should tend to make them similar in behavior. Consequently we cannot say that environment alone was responsible for their criminal behavior

In most cases the crimes were not committed by the twins in company. Nevertheless, the type of crimes committed by the pairs of identical twins, as well as the general behavior of the two individuals, showed much greater resemblances than in the case of fraternal twins The higher degree of similarity in the behavior of the identical twins can best be explained as due to their greater similarity in heredity

The foregoing studies strongly suggest innate differences in susceptibility to the temptation to commit crimes It is clear, however, that the environment is an important factor in causing one to yield to the temptation or to resist it. The general conclusions from these investigations are supported by the most extensive studies of twins so far made in the United States: the work of Professor H H Newman and two of his colleagues at the University of Chicago In an extremely interesting book[2] containing the results of more than ten years of labor the authors describe exhaustive measurements and tests of 119 pairs of twins. The monograph, containing many tables, graphs, and a carefully reasoned analysis of the data, cannot be too highly recommended to those interested in the problem of heredity and environment as it applies especially to the normal physical and mental differences in man.

The first part of the book contains a comparison of paired differences of 50 pairs of identical twins reared together with 50 pairs of fraternal twins of the same sex also reared together. If one assumes that the environment of fraternal twins is about as uniform as that of identical twins, the differences between the interpair differences in the two groups should be an expression of the force of heredity.

[1] A. J. Rosanoff, L M Handy, and I. A. Rosanoff, Criminality and Delinquency in Twins, *J. Criminal Law Criminol*, 24:923, 1934

[2] Horatio H Newman, Frank N Freeman, and Karl J. Holzinger, "Twins. A Study of Heredity and Environment," University of Chicago Press, Chicago, 1937.

The examination given the 100 pairs of twins reared together included the following observations and tests

PHYSICAL OBSERVATIONS AND MEASUREMENTS

Height, standing and sitting
Weight
Head length and width
Cephalic index
Hair color and texture
Hair whorl (location and direction of twist)
Eye color and pigment pattern on the iris
Skin texture and coloration
Handedness
Palmprints and fingerprints
Ears, general contour and peculiarities
Other facial features
Birthmarks, moles, etc.

TESTS

Standard Revision of the Binet-Simon Test of Intelligence
Otis Self-administering Test of Mental Ability
Stanford Achievement Test
Downey Will-Temperament Test (parts dealing with speed of decision, coordination of impulses, motor inhibition, and finality of judgment)
Woodworth-Mathews Questionnaire
Tapping tests for the objective determination of handedness

Information was gathered, also, by interviews with parents and others regarding age, physical history, school history, general interests, and talents

A comparison of the average differences in some of the traits measured is shown in Table 16

TABLE 16 MEAN PAIR DIFFERENCES IN SELECTED TRAITS FOR 50 PAIRS OF IDENTICAL TWINS AND 50 PAIRS OF SAME-SEXED FRATERNAL TWINS*

Selected traits	Identical (reared together)	Fraternal (reared together)
Standing heights	1 7 cm.	4.4 cm
Weight	4 1 lb	10 0 lb
Head length	2 9 mm.	6 2 mm
Head width	2 8 mm.	4 2 mm.
Cephalic index	0 016	0 028
Total finger ridges	5 9	22 3
Total motor score	19 3	29 0
Binet IQ	5 9	9.9
Otis IQ	4 5	9 3
Stanford Educational Age	6 4 mo.	11 6 mo.
Woodworth-Mathews Questionnaire	5 3	6 7

* After Newman, Freeman, and Holzinger.

In the case of heights, weights, and Binet IQ, the differences were also compared with differences among ordinary brothers and sisters of the twins Differences among the latter were found to be almost exactly the same as among fraternal twins

The first point to be noted is that identical twins are not absolutely identical in any of the traits listed Evidently, environmental differences, either prenatal or postnatal, are sufficient to produce measurable differences—in some cases fairly great ones—in identical twins reared in the same home. The differences between identical twins, however, are seen to be only about half as great as those between fraternal twins Unlike genes obviously account for the greater differences in the fraternal twins

Of the traits listed in the table, the one in which heredity appears to be relatively most influential is total finger ridges This is in keeping with the finding that physical traits as a group show relatively great influence of heredity and less influence of environment than the mental traits The authors' explanation of this rule is as follows·

A most plausible provisional hypothesis would seem to be that behavior and mental ability are more subject to the influence of training and environment than are physical size, form, and features, such as color of eyes, color and texture of hair, etc. It is quite plausible to suppose that the nervous system, which is the physical counterpart of mental traits, of behavior, and of abilities, being more subject to influence by stimulation from the external world, is also more susceptible to variations through such stimulation and through the responses which are made to it.

But, one may ask, why should identical twins, having identical sets of genes and reared in the same home, show even this much difference? The answer, according to the authors, is, in part at least, differences in the prenatal environment:

It is commonly believed that one member of each pair of identical twins is lacking in vitality as compared with the other Many even believe that one member of each pair is sterile While such views as these are incorrect, there seems to be some basis for the general impression, for in many cases one member of a pair of twins actually is physically inferior to the other in many ways from the time of birth on It seems probable that such early differences in vigor and vitality are the result of minor inequality in the fetal blood supply of the twins, resulting from an imbalance in the placental blood exchange

That this imbalance in blood exchange does produce marked differences in surviving twins is evidenced by the fact brought out by the extensive observations of Schatz, who found that, at about the middle period of pregnancy, size differences in monozygotic [one-egg] twins average much greater than in dizygotic [two-egg] twins This is the opposite of what might be expected on a genetic basis Identical twins that survive this period tend to be more nearly equal in size, but even at birth their size differences equal on the average those of dizygotic twins, many of the former showing more marked differences than the

average of the latter. As has been said, such size differences frequently persist for life, and it seems probable that differences produced by this prenatal factor extend beyond mere size and involve also differences in vigor and general health. How much of the observed size and weight differences in adult identical twins trace back to the factor under discussion we have no means of knowing, but it seems obvious that the effects of this factor are too important to be ignored In concluding discussion of this factor it should be emphasized that it is peculiar to monozygotic twins, for there are no known cases of dizygotic twins in man in which placental anastomoses of fetal blood vessels occur.

The *prenatal* environment of a pair of fraternal twins thus shows on the average greater uniformity than that of a pair of identical twins This tends to balance the greater uniformity of the *postnatal* environment of identical twins.

Identical Twins Reared Apart

The really unique phase of the work of Newman et al on twins, as well as the part which presented the greatest difficulties, was the discovery and study of 19 pairs of identical twins separated in infancy and reared apart In order to secure the number needed for statistical treatment the country was combed by letter, newspaper, and radio—the latter medium, incidentally, proving far the most effective

The peculiar advantage in the study of identical twins reared apart is that they constitute a natural experiment in which one factor, heredity, is constant, while the other factor, environment, is varied Therefore the differences found (or rather that part of the differences in excess of the differences in identical twins reared together) should be due to the environment By studying the differences in the environment of separated twins the effect of various factors in the environment may be discovered

As a control on the environmental side there were already available to the authors the 50 pairs of identical twins reared together, in which the environment was as uniform as it is possible to find.

Extreme similarity was found among identical twins reared apart in the following physical traits hair color and hair texture, eye color and pigment pattern of the iris, skin texture and coloration (except in a few cases where differences in health or exposure had produced noticeable differences), and shape and size of ears, nose, mouth, lips, chin, and teeth In these traits the environmental differences encountered had practically no effect In a number of other physical characteristics, however, considerable differences were found. A comparison of the differences in identical twins reared together with those reared apart is shown in Table 17.

It is obvious that the differences between the means of the two groups of twins are much greater for some traits than for others. By applying the usual statistical methods the authors calculated that the differences were significant only for weight, Binet IQ, Otis IQ, and Stanford Achieve-

ment. For traits such as height and head measurements no significant difference appears The writers cautiously state·

These latter findings are as important as the former in that they indicate traits *unmodifiable* by the type of environmental change here studied All these inferences are, of course, limited by the small number of separated cases and the *small* environmental difference by twin pairs for a considerable proportion of these . . . Fifteen of the pairs had only a moderate variation in environment, whereas *four* pairs were reared in extremely different surroundings If the contrast in environment had been greater for all cases, the influence of this factor would have been much larger.

TABLE 17. MEAN PAIR DIFFERENCES IN SELECTED TRAITS FOR TWO GROUPS OF IDENTICAL TWINS*

Selected traits	Identical (reared apart)	Identical (reared together)
Height	1 80 cm	1 01 cm
Weight	9 90 lb	4 03 lb
Head length	2 20 mm	2 59 mm
Head width	2 85 mm	2 25 mm
Binet IQ	8 21	5 35
Otis IQ	8 00	4 54
Stanford Achievement	16 26 mo	6 38 mo
Woodworth-Mathews Questionnaire	5 00	5 48

* After Newman, Freeman, and Holzinger

After proper comparisons of data, it was concluded that educational and social differences in environment were effective in producing variations in such traits as intelligence and school achievement, and possibly some slight changes in temperament; while variations in physical environment were responsible for changes in weight, and to some extent in temperament.

A general conclusion as to the relative importance of heredity and environment is contained in the following quotation.

The analysis indicates that the role of heredity and environment in producing twin differences is a function of the type of environment Thus, for twins reared together, most of the difference between members of a pair may be due to the nature factor; whereas for twins reared under strikingly different environments, the nurture factors will have a relatively greater influence.

It is apparent from several of the comparisons made that the relative effect of hereditary and environmental differences is also a function of the type of trait Any fixed ratio of these two factors for all traits and conditions is thus impossible. We must consider their relation always in connection with the kind of trait and grade of environmental difference.

From the viewpoint of the educator it is important to note that extreme differences in educational and social environments are accompanied by significant changes in intelligence and educational achievement as measured by our tests

A large part of the book is devoted to detailed case studies of the 19 pairs of identical twins reared apart. The case studies suggest striking relations between certain factors in the environment and some of the characteristics The pairs brought up under the most divergent conditions are of greatest interest, as illustrated in the two cases briefly described below. It is such cases that emphasize the power of the environment in causing differences.

1. *Gladys and Helen* were both married women, 35 years old when examined They were born in Ohio and after being separated at 18 months of age did not meet again until they were 28

Gladys was reared in a medium-sized city in Ontario, Canada When she had finished the second grade, her foster father, who was a railroad conductor, went to the Rocky Mountains for his health. Gladys was taken along. There were no schools, and when after two years the family returned to Ontario, she did not reenter school but remained at home doing housework

At 17 she went to work in a knitting mill, at 19 she began work as a saleswoman in Detroit, working at this and at clerical work for a number of years For the nine years preceding the tests she had been an assistant to the head of a small publishing house in Detroit, where her duties consisted of setting type, writing copy, and proofreading.

Helen's foster parents were farmers in southern Michigan. She was not required to work hard at home and was sent to a good Michigan college where she received a bachelor's degree Soon afterward she began teaching school, and for the eight years preceding the tests had been teaching in a large school in Detroit.

In weight, the sisters were almost identical, but Helen was 1.1 inches the taller. In other physical traits the two were very similar. In both twins the terminal joint of the index finger of both hands was bent toward the thumb in a curious fashion—an example of the sort of nonadaptive resemblance commonly found in identical twins and constituting good evidence of identical heredity

As might be expected from their differences in schooling, Helen was far superior to Gladys in all the mental tests. In the Stanford-Binet test the difference was 3 years 10 months, or 24 points in IQ. The differences in test intelligence were greater for this pair than for any other pair reared apart; the difference in formal education was also greatest in this pair.

With respect to personality differences the authors make the following comment:

Observations of the overt behavior of these twins revealed some further important personality differences. Helen is a confident and suave person with rather marked charm of manner. She makes the most of her personal appearance, moves about gracefully, and is apparently conscious of making a favorable impression on men. She conversed smoothly without a trace of diffidence and always took the lead in all matters pertaining to arrangements for the trip and the stay in Chicago. One sees at once that she is by far the more aggressive in her overt acts, but the Downey test revealed about equally strong aggressiveness in the two women. Gladys made the impression upon us of a person ill at ease. This attitude may have been partly the result of a feeling of inferiority in view of the apparent certainty that she would make a comparatively poor showing on the tests. She seemed to us to be a rather staid and stolid person, distinctly diffident. She had no affectations to match those of her sister and had no charm of manner or grace of movement. She was not becomingly dressed nor did she make the best of her physique. She never volunteered any information and was difficult to draw into conversation. She made no effort to create a favorable personal impression. In general, the contrast in overt behavior during social contacts was rather extreme.

As an advertisement for a college education the contrast between these twins should be quite effective.

2. *James and Reece* were 27 years old when examined. They were born in a mountain village in southeastern Tennessee. Their mother died in childbirth and they were separated at less than one year of age, James being taken by his maternal grandparents and Reece by his paternal grandparents. Because of strained relations between the two foster families, the twins never associated. Until their visit to Chicago they had never spent more than a few hours together.

After graduating from high school James was employed as an engineer in a sawmill and sand-and-gravel business run by his grandfather and maternal uncle, who were reported as steady and industrious people.

The paternal grandparents with whom Reece lived were "mountaineers of the more primitive sort, a type common in the mountains of Tennessee." The grandfather, a Confederate veteran with a pension almost large enough to live on, had never worked steadily, but had tried his hand at coal mining, blacksmithing, and work on the railroad. Reece followed the custom of the family in avoiding regular work. For a short time he worked in an automobile factory, but that was "too much like slavery" to him, so he returned to the mountains. The authors state that it would not be fair to recount any of his less creditable occupations and experiences.

Reece attended a mountain school when he felt so inclined, but never for more than five months in the year, usually much less. He completed the eighth grade. The authors do not feel free to divulge the details of his social environment but state that the contrast with that of his brother was very great.

Both men were married early James had had two children, one of whom died in infancy; Reece had none The authors state: "Steady work, largely in the open, on the part of James, and the free life in the mountains, except when he was not so free, on the part of Reece, seem to offer no great contrasts from the purely physical standpoint"

In physical appearance these twins were as similar as the average pair of identical twins reared together, although James weighed 14 pounds more than Reece. Among their striking similarities the following are mentioned by the authors. "Both have the same peculiar iris pattern—a very dark outside ring surrounding a greenish-brown center. Both left eyes are slightly strabismic and have no image-forming power, merely reacting to light and darkness . The fingernails of both have been bitten down to an extreme extent" It is interesting to note that in one other pair of identical twins reared apart (two boys of 19), the fingernails of both were bitten down in the same way.

According to the authors, "An unusual feature that is present in the pen writing of both, but does not appear in the pencil writing, is a rather marked tremor This doubtless has a physiological basis, but we are unable to say what it is" In other respects, however, the handwriting showed marked differences.

In intelligence, James ranked 19 points above Reece in IQ on the Binet Scale—the second largest difference found among separated twins The difference was as great on the International Test as on the others

In summarizing the personality of the twins the authors write:

> The facts regarding personality are not so simple. In some basic elements of temperament these brothers, brought up under such diverse conditions, are remarkably similar This is brought out most strikingly in the Downey Test In the tests of neurotic disposition and of emotions, also, they are rather similar In behavior, judged from the point of view of its social productiveness and acceptability, however, the contrast is sharp. There is also a marked contrast in handwriting. While, then, a certain basic similarity in mode of reaction exists by nature and persists in spite of differences in the environment, some rather fundamental modification has apparently been made, and marked effects in the aim, direction, and content of behavior are obvious

The differences in behavior in this pair of twins are interesting when compared with the studies of twins in Germany, referred to previously

AGE OF MOTHER A FACTOR IN MAMMALS

In most respects the uterine environment of mammals is well standardized. Within a given species there is probably little variation in embryonic environment in such ordinary factors as temperature, light, and moisture. With respect to food and the chemical environment in general, however, there are possibilities of differences. It is therefore not surpris-

ing to find that the age of the mother is sometimes an important differentiating factor among the offspring of mammals

There is a popular belief that many differences among children in human families are due to the age of the mother or to the father So far as the father is concerned there seems to be no good evidence in support of such a belief, either from animal breeding or from the study of human families The male affects the offspring only through the sperm, and a sperm seems to be little more than an animated package of genes The genes carried by the sperms are apparently not affected by the age of the male that produces the sperms.

On the other hand, the mammalian female has an intimate relationship to the developing embryo, since substances in the mother's blood are constantly diffusing into the blood of the embryo It is reasonable to suppose that advancing age may cause changes in the composition of the blood, thus making the environment of embryos in older mothers somewhat different from that of young mothers

So far as is known, the only experimental studies in animals showing an unmistakable effect of age of mothers upon offspring are those reported by Sewall Wright [1] In an extensive experiment with guinea pigs he found that in a family of purebred animals having a piebald (white-spotted) pattern, the percentage of white skin and hair of the offspring increased with the age of the mother until the mother had reached her full growth.

In this same family of guinea pigs there was a hereditary tendency to produce offspring with a fourth toe on each hind foot (Most guinea pigs have only three toes on each hind foot) It was found that this tendency decreased to a remarkable extent with increase in age of mother This relationship is shown in Table 18, below

TABLE 18 EFFECT OF AGE OF MOTHER ON NUMBER OF TOES IN GUINEA PIGS*

Age of mother, mo	Number of young	Per cent with fourth toe
3–6	349	52 7
6–9	390	40 0
9–12	310	29 2
12–15	292	26 7
15–21	330	18 5
21–46	296	14 2
Total	1,976	31 1

* After Wright

[1] Sewall Wright, Effects of Age of Parents on Characteristics of the Guinea Pig, *Am. Naturalist*, 60:552–559, 1926

The experiments on extra toes do not rule out entirely the possible effect of the age of the father, since in the great majority of the matings the father was of exactly the same age as the mother. Yet the few cases of marked difference in age of parents all pointed toward the importance of the mother in this respect The most interesting of these cases was the birth of a litter when the female was only 100 days old. This litter was sired by an adult male 17 months old The three offspring had fourth toes In two the fourth toes were perfectly developed; in the other almost perfectly so.

In this family of guinea pigs only 29 cases of perfect fourth toes had been recorded among 1,976 animals, 14 of these were born before the mother reached her sixth month. The author concludes, "it can hardly be a coincidence that the most perfect polydactylous litter in the entire body of data was produced by the youngest dam."[1]

Why should young mothers produce offspring with more pigment and more toes than older mothers? We do not know. Wright suggests that possibly some sort of competition between the growth process of the mother and the early developmental processes of the embryo may be responsible, since guinea pigs have reached only about half their mature weight at three months of age and do not reach their full growth until about fifteen months It is possible that a decrease in the rate of metabolism in the female, with advancing age, may be a factor—a higher rate of metabolism in young mothers favoring the production of pigment and extra toes

Whatever the cause of greater frequency of four-toed offspring from young mothers, it is clear that there is no difference between the genes transmitted by young mothers and those transmitted by older mothers. Wright found that females born to young mothers produced the same percentage of four-toed offspring as females born to older mothers Moreover, it was found that three-toed parents produced the same percentage of four-toed offspring as four-toed parents. In this inbred and largely homozygous family the three-toed and the four-toed individuals were genetically alike, in both cases transmitting merely a tendency to develop a fourth toe under certain conditions There was no evidence whatever of inheritance of an acquired characteristic: the occasional occurrence of four toes is an environmental effect that lasts for only one generation.

The extra toe in guinea pigs is an excellent example of the interaction of heredity and environment. In some pure breeds of guinea pigs the fourth toe never develops, in one breed obtained by selection by Professor W. E. Castle, of Harvard University, the fourth toe always develops.

[1] In a later study Wright showed that the age of the father has no effect upon the frequency of fourth toes in the offspring *Genetics*, 19:537–551, 1934

Obviously we are here dealing with a clear-cut hereditary difference in the breeds Crossing experiments between the pure three-toed and pure four-toed breeds indicate that the fourth toe depends upon several recessive genes Incidentally, the fourth toe is not a duplication of an existing toe, but in structure and position corresponds to the little toe in other mammals It is thus highly probable that it is a restoration of an ancient ancestral condition.

Suppose that we had never heard of these other families of guinea pigs, but knew only of the family studied by Wright. We would then certainly be inclined to say that the extra toe is largely an environmental difference, but from our consideration of the species as a whole, we must conclude that it is both hereditary and environmental

If all three families had been allowed to breed indiscriminately in a breeding pen, we would have had difficulty in deciding as to the relative importance of the two factors—heredity and environment—in determining the number of toes in the offspring The resulting confusion of factors would be analogous to the situation in man where the heterogeneous nature of the population presents great obstacles to the study of heredity and environment. As a means of avoiding such obstacles the study of human twins has proved to be an extremely valuable method

AGE OF MOTHER A FACTOR IN MAN MONGOLISM

We have noted in Chap 9 that the age of the mother is an important factor in the production of human fraternal twins This may mean simply that in older women two eggs are more often released from the ovary at one time than in younger women There is, however, a well-known case in man in which the characteristics of the individual offspring are affected by the age of the mother This is the condition known as *Mongolism* (Fig. 69). Detailed descriptions have been published by various authors, including Rosanoff[1] and Penrose,[2] whose descriptions are the basis of the following brief summary.

The name *Mongolism* was coined by J. Langdon Down, of London, in 1866 for a definite kind of mental defective that has as a common trait a fold of skin on the upper eyelid similar to that of Mongoloids (Fig 119) Other common characteristics of affected individuals are relatively short stature and light weight; unusually small round head, late and irregular eruption of teeth, tongue relatively large and often deeply fissured; hands small, broad, and stubby; low muscular tone and laxity of the joints; in

[1] Aaron Rosanoff, "Manual of Psychiatry and Mental Hygiene," 7th ed, John Wiley & Sons, Inc., New York, 1938

[2] Lionel S. Penrose, "The Biology of Mental Defect," Grune & Stratton, Inc., New York, 1949.

infants, late development of the power to hold up the head, sit up, and walk (often unable to walk until after three years of age); mouth breathing, with a marked susceptibility to respiratory infections; congenital heart anomalies in at least 20 per cent of the cases; circulation to the extremities poor, with undue sensitiveness to extremes of heat and cold; genitalia infantile, secondary sex characters late in appearance and incomplete in development, sex interest slight or absent; failure to learn



Figure 69. Mongolism in two imbecile brothers aged 10 and 5 years (*left*) with a normal child aged $2\frac{1}{2}$ years (*right*). (*From Penrose, "The Biology of Mental Defect," Grune & Stratton, Inc.*)

to talk in at least 25 per cent of the cases, in the others talking learned slowly and imperfectly. Penrose states that almost all the signs of Mongolism are indications of retarded development. He gives the mean IQ for institutional cases as 20 to 25. Behavior difficulties are rare and patients are quiet, cheerful, and affectionate

Very few sufferers live to be adults. According to Penrose the expectation of life at birth is about nine years.

A number of statistical studies have been made on the frequency of Mongolism In populations of European origin one birth in 500 to 1,500 is a Mongoloid Among Negroes the frequency seems to be much lower

There have been many theories advanced as to the cause of Mongolism, among them heredity. Some workers, however, have denied that heredity has anything to do with it. In the latter group are Benda,[1] and

[1] Clemens E. Benda, "Mongolism and Cretinism," Grune & Stratton, Inc., New York, 1949.

Rosanoff, who takes this view because—in contrast to other forms of mental deficiency—there is rarely more than one case of Mongolism in a single family. Studies indicate, however, that at least 1 per cent of mothers of Mongoloids also have a second Mongoloid [1] This, of course, does not prove that Mongolism is hereditary

It is now demonstrated that the age of the mother is an important factor in the occurrence of the defect Numerous studies have shown that most cases of Mongolism come from mothers well along toward the end of the reproductive period. The average age of mothers of Mongoloid defectives is about 37 years, while that of mothers of normal children is about 29 years. In mothers under 25 the incidence of Mongoloid births is about 0 5 per 1,000; from ages 25 to 34 it is about 0 8 per 1,000, 35 to 39 about 2 8; 40 to 44 about 7 6; and from 45 to 49 it reaches 27 5 per 1,000 (Penrose) Penrose finds that the age of the father has no effect upon the frequency of Mongolism.

The incidence of Mongolism in twins is in entire agreement with the theory of heredity as a factor in the production of Mongoloids Note that in every case of Mongolism listed in Table 19 both identical twins of a pair are affected if one is affected, while in every pair of fraternal twins only one member is affected This concordance among identical twins and lack of concordance among fraternal twins is exactly the distribution found in other rare characteristics known to be hereditary No specific genetic mechanism, however, has been established

TABLE 19 SUMMARY OF CASES OF MONGOLISM IN TWINS PUBLISHED UP TO 1935*

Type of twins	Number of cases	One affected	Both affected
Identical, males	3		3
Identical, females	5		5
Same-sex, fraternal, males	6	6	
Same-sex, fraternal, females	7	7	
Opposite-sex, fraternal	23	23	
Total.	44	36	8

* After Rosanoff

It seems probable, therefore, that the susceptibility to Mongolism is inherited, just as is the tendency to develop the fourth toe on the hind foot of guinea pigs, as described in the preceding section In both cases the exact mode of inheritance is still unknown. As women grow older there may be some change in the chemical condition of the blood, per-

[1] J. A Book and S C Reed, Empiric Risk Figures in Mongolism, *J. Am Med Assoc*, **143**:730–732, 1950

haps a hormone deficiency or the accumulation of certain metabolic products, which, in cooperation with particular genes, causes the development of Mongolism

Harelip and harelip associated with cleft palate have recently been found to increase greatly in frequency with the advancing age of the mother (see Chap. 15)

ARE ACQUIRED CHARACTERISTICS INHERITED?

In considering this much-debated question it is most important to define our terms carefully. From the preceding discussion it is clear that in one sense every characteristic of the individual is acquired, since in each generation characteristics develop anew under the combined influence of genes and the environment. It is also clear from the study of life on earth that over a period of many generations a species gradually acquires new hereditary characteristics. This is not what is ordinarily meant, however, when the expression *acquired characteristics* is used.

The inheritance of acquired characters has come to have a particular meaning developed especially by the French biologist Lamarck (1744–1829). Lamarck observed that animals have certain needs that must be satisfied if the individual is to survive. The urge to satisfy these needs leads the animal to act. Activity involves the use of muscles The exercise of a muscle stimulates its growth, failure to use a muscle results in atrophy

Lamarck assumed that changes due to use and disuse were inherited; consequently the offspring produced after the change should start out where the parent left off. This process of use, individual development, and inheritance, repeated generation after generation, should cause the species to become better and better adapted to its environment. And such adaptive changes would in time result in the origin of a new species

Thus the giraffe, a browser on the leaves of trees, is known to stretch the neck and tongue to reach the leaves (Fig. 70). Such exercise, according to Lamarck's hypothesis, causes the neck and legs to grow in length The increased length is inherited by the young, which in turn stretch their necks, feed, and grow, finally transmitting their increased height to their own offspring Thus in time there evolves a giraffe standing 18 feet in height, according to the theory.

The hypothesis of the inheritance of acquired characters sometimes goes under the name *Lamarckism*, although the belief is very ancient Hippocrates, born 460 B.C., famous Greek physician and honored as the Father of Medicine, accepted the idea. So did Aristotle to a lesser degree

Although the inheritance of acquired characters was widely accepted in Mendel's day—accepted, indeed, without any valid substantiating evi-

dence—it has now been abandoned by practically all biologists except those in the Soviet countries, mentioned below The theory necessarily implies a mechanism of some sort whereby any change in the body cells produced by the environmental conditions will register a specific effect



Figure 70. This giraffe was found stretching its neck to the utmost in order to reach the leaves on the tree Hay was available to the animal with no effort on its part (*Photograph by the author.*)

in the reproductive cells in such a way that the offspring will develop the new characteristic without themselves being exposed to the original conditions.

Charles Darwin thought that the effects of use and disuse of structures in animals and the direct effects of the environment in plants were inherited. Consequently he felt the need of a mechanism for transferring such effects to the reproductive cells As a purely imaginary concept he proposed what he called the *hypothesis of pangenesis*, wherein he suggested that the cells of each part of the body liberated into the blood

minute granules with the power to multiply and accumulate in the reproductive cells In the offspring these particles were supposed to cause the development of cells like those from which they came

No evidence, however, was ever found in support of the hypothesis of pangenesis, while the evidence from subsequent discoveries relating to mitotic cell division, the process of sperm and egg formation, chromosome constitution, and genes convinces us today that the facts are essentially opposed to Darwin's theory We now look upon development as proceeding outwardly from the genes, the genes producing their effect upon the body cells but being unchanged by the usual processes of differentiation of the body cells The end result, i e , the characteristic, may be influenced by the environment and by use and disuse, but these influences have no power to bring about a specific change in the gene

A second important reason why the inheritance of acquired characteristics has hardly any supporters among biologists today—excluding those living under the Soviet system—is the negative result of countless experiments with plants and animals Although from time to time up to recent years experimenters have thought that they got positive results in the offspring by training or specific environmental treatment given the parents, not one of these experiments has stood the test of critical examination and repetition at the hands of other experimenters Darwin seems to have accepted Lamarck's theory on the basis of reported positive results by various experimenters Unfortunately, he did not repeat the experiments himself and thus did not discover his error. As mentioned in Chap 1, Mendel performed certain experiments with plants which made him skeptical of Lamarckism

The countries under the Soviet system are exceptional in that Lamarck's hypothesis of the inheritance of acquired characters is there officially accepted. Until a few years ago much study, research, and teaching of Mendelian genetics could be found in Russia In 1948, however, in the U S.S R Mendelian genetics was officially repudiated,[1,2] and research institutes and educational institutions were ordered to follow the teachings of a former plant breeder Michurin and his leading present exponent T. D. Lysenko One of the principal tenets of these plant breeders is the inheritance of acquired characters. Lysenko has also expressed ideas similar to those of Darwin's hypothesis of pangenesis, as an explanation of the supposed Lamarckian effect. No convincing evidence of Lamarckism, however, has been presented by Lysenko and his followers Repetitions of some of their experiments have been done in England[3] and in the

[1] Julian Huxley, "Heredity, East and West," Abelard-Schuman, Inc., Publishers, New York, 1949.

[2] Conway Zirkle (ed), "Death of a Science," University of Pennsylvania Press, Philadelphia, 1949.

[3] L. Sachs, Vegetative Hybridization in the Tomato, *Nature (London)*, 167:282–283, 1951.

United States,[1] and no confirmation of the claims of Soviet biologists has been obtained.

As we look at the problem from all sides today, it is perhaps fortunate for the offspring that the reproductive cells of the parents are so well protected from the effects of the activities of the parents and from the influence of the environment, and that each generation can start with a clean slate, instead of inheriting all the acquired characteristics, bad as well as good, of their parents.

But if the effects of use and disuse and the ordinary environmental factors are not inherited, how are we to account for the multitude of hereditary characteristics which complex organisms possess? How do genes change, and how are new genes added? These are questions which we shall attempt to answer in the following chapter.

"MENTAL IMPRESSIONS" (MATERNAL IMPRESSIONS)

Most women perhaps would like to believe that by voluntarily controlling their thoughts and actions they could influence for the better their unborn children Many fear that mental shocks, such as the sight of some abhorrent object, received during the period of pregnancy will have specific effects upon the child. Birthmarks of various kinds as well as serious abnormalities have been attributed to such experiences Ancient as are these beliefs and reputable as are some of the scientists who in earlier days accepted them, there is today no reason for such fears and beliefs

No good evidence has ever been produced to prove the transmission of mental impressions What purports to be evidence invariably turns out to be isolated instances of abnormalities of development coupled with a recollection of some peculiar experience of the mother, supposed by her to be the cause of the abnormality. The kind of evidence needed to show the inheritance of maternal impressions—evidence which seems to be wholly lacking—is records of experiences by women made *before* the birth of the infant, with the observation of marks fitting such experiences The belief in maternal impressions rests upon the fallacious reasoning that because one event follows another, the second event must be caused by the first.

Not only is there no good evidence that mental impressions occur, but there are good biological reasons why they cannot occur. In the first place, the nervous system of the developing child has no direct connection with the nervous system of the mother. The child is connected to the placenta of the mother by the umbilical cord only. Blood vessels, but no nerves, lie in the cord Secondly, the blood of the mother normally does not pass directly into the blood vessels of the embryo; the vessels of the

[1] A. B Burdick, Experimental Evidence Relating to One Postulate of the New Russian Genetics, *Records Genet Soc. Am.* (abstract, p 14), 1952.

two merely lie side by side, permitting substances from the mother's blood to diffuse through the walls of the blood vessels into the blood of the embryo It is only certain chemical changes in the mother's blood, or the presence of particular parasites, that have been proved to have an effect on her unborn child In the former category, of course, come poisons of various kinds, a diet deficient in vitamin D, and antibodies (a striking example of which exists in the Rh blood factor, considered in a later chapter) Among the specific microparasites that are known to affect the embryo by way of the placenta are the spirochete of syphilis and the virus of German measles (rubella). A severe attack of rubella during the first three months of pregnancy may produce serious damage to the eyes, ears, heart, or brain of the child

Other changes in the blood of the mother of a more subtle nature are no doubt responsible for a few variations in individuals. For example, we have already considered the age of the mother as a factor in the development of Mongolism.

PROBLEMS

1. If the effect of environmental factors in determining differences is to be studied, what should be the genetic make-up of the individuals used in the study?

2. If the effect of alternative genes in determining differences is to be studied, what should be the nature of the environment of the experimental individuals?

3. In human beings the external environmental factors such as light, temperature, and food have no obvious effect upon the color of the eyes. Does this mean that the development of the eye color in the individual is independent of all environmental factors? Explain.

4 Give several reasons why in mammals it is more difficult to demonstrate hereditary differences in behavior patterns than hereditary differences in physical traits

5. Why are identical twins reared apart especially favorable material for the study of the roles of heredity and environment?

6. The statement is sometimes made that differences in intelligence in man are not due to heredity if the individuals compared are normal and healthy. Analyze critically this statement and state your own conclusions on the question of the relationship between heredity and intelligence.

7. Assuming that all the cells in the body contain identical sets of genes (the evidence available indicates that in general this is true), to what may we attribute the differentiation of the cells into muscles, glands, skin, brain cells, etc.?

8. If the genes in all parts of the body are identical, how may we account for the fact that paired structures on opposite sides of the body, e g, fingerprint patterns, shape of ears, etc., are never absolutely identical?

9. Aside from humanitarian reasons, and purely for genetic reasons, why should the environmental conditions for all the people be made as favorable as possible, under a program designed to improve the hereditary qualities of a people?

10. What human characteristics are clearly influenced by environmental differences, judging by the results of the studies of identical twins by Newman and his associates?

11. Does the fact that no significant differences were observed in height and head shape prove that these characters are not affected by differences in food or other environmental factors? Explain and if possible give examples

12 What are some of the reasons for rejecting the hypothesis of the inheritance of acquired characters?

13. What reasons can be given for disbelief in the existence of maternal impressions?

12

THE GENE AND MUTATION

Hugo De Vries, famous Dutch botanist, remembered as one of the rediscoverers of Mendel's work, brought into general use the word "mutation." He did this by writing a book entitled "The Mutation Theory," published in 1901. His views are summarized in the following quotation:

These saltations, or mutations, of which the so-called sports are the best known instances, constitute a distinct province in the study of variability. They occur without transitional gradations and are rare; whilst ordinary variations are continuous and always present. . . . Mutations give rise not only to species but also to varieties.

In thus emphasizing the discontinuous nature of mutations and the difference between mutations and ordinary variations (by which he meant environmental variations), De Vries made a significant contribution to the study of evolution. His experiments, observations, and writings aided much in discrediting the theory of the inheritance of acquired characteristics.

But, according to Professor Thomas Hunt Morgan,[1] pioneer in the study of heredity in the United States,

it was not so much the idea that variation is a discontinuous process that makes de Vries's contribution significant. It was rather, as he thought, his detection of the process of mutation at work, and his demonstration that it is playing a rôle in the evolution of certain forms living today. Here, if de Vries was correct, was a chance to study by direct observation and controlled experiment the processes by which evolution of animals and plants comes about. . . . The sequel has, I think, justified the expectation. . . .

De Vries observed that mutations are often indifferent, neither helping nor hindering their possessor, and he assumed that indifferent mutations as well as beneficial ones might become fixed in the population. If true, this would account for the fact that closely related species frequently differ in nonadaptive characteristics; these cannot be accounted for by natural selection, since natural selection changes species in adaptive ways

[1] Thomas Hunt Morgan, "The Scientific Basis of Evolution," 2d ed., W. W. Norton & Company, Inc., New York, 1935.

The cause and the physical basis of De Vries' "mutations" were unknown; De Vries, therefore, used the term mutation to include all hereditary changes. The word is still much used in this comprehensive sense, although there is a tendency in the United States to restrict its meaning to a change in a single gene. Other kinds of hereditary changes—of which there are many, such as duplications or losses of entire chromosomes or chromosome sets or pieces of chromosomes, or gross reorganization of chromosomes—are designated *chromosome changes* As a matter of fact, some of these chromosome changes are transmitted in the same way as gene mutations Consequently, many supposed gene mutations may turn out to be chromosome changes, as some actually have in the past In general, any Mendelian change is regarded as a gene mutation until it is shown to be the result of some gross chromosome change Most of the so-called mutations which De Vries observed proved later to be chromosome changes.

De Vries looked upon mutations as changes which cause large and conspicuous effects (as most chromosome changes are known to do), but as more refined methods for the study of mutations were developed, it became clear that the fundamental thing about the phenomenon is the change in the gene—not the size of the effects Gene mutations may produce effects varying all the way from large and conspicuous ones down to those that are barely perceptible, and perhaps even imperceptible by our present methods of observation This is easily illustrated in man: the mutant genes for albinism and for amaurotic idiocy, to choose two examples, produce gross changes in various parts of the body, while some other genes, such as those responsible for the large number of slight differences in the shade of the hair, produce small effects Although it has not been proved that albinism and amaurotic idiocy are due to gene mutations rather than to chromosome changes, the principle holds good, nevertheless, since many examples could be cited for plants and animals in which the effects of gene changes are either great or minute

Recent investigations in several directions indicate that small mutations are the most numerous of all In agreement with this conclusion, the analysis of related species in plants and animals, by crossing and otherwise, shows that their differences depend upon many mutations, each of which by itself has only a slight effect. Consequently, Darwin's formula for the origin of species by the "accumulation of innumerable slight variations" is perhaps not far from the truth in the great majority of cases

On the basis of what has been said above we may define a mutation as a sudden and discontinuous change in a gene, occurring rarely for any particular gene, and capable of producing a change—great or small—in some part of the body. Mutated genes possess in general the same degree of permanency as the original genes from which they came.

THE NATURE OF THE GENE

Genes occupy a position today similar to that occupied by vitamins, hormones, and enzymes a few years ago; that is, we know that genes exist, we know where they reside, we know much about their effects, but no one has yet been able to isolate and analyze them chemically or to produce them synthetically, as can be done with many of the vitamins and hormones

Based upon indirect evidence, the theory most widely accepted today is that genes are specific chemical substances having certain physical, chemical, and physiological properties in common. One of their most interesting properties is that of aiding in the formation of enzymes, which in turn play specific roles in the metabolism of the cells. For example, in the Himalayan rabbit (page 187) a gene causes the formation of an enzyme which is essential in the synthesis of melanin pigment.

Many investigators think that genes are large nucleoprotein molecules (Fig 71) The prevailing view now is that gene *specificity* depends on the nucleic acid component (desoxyribose nucleic acid, as far as known, except in the plant viruses). These ideas are in harmony with two discoveries: first, that certain disease-producing viruses are large nucleoprotein molecules, and second, that genes and viruses show a number of interesting properties in common.

As to their common properties, both genes and viruses are minute bodies of comparable size (Fig 72); both multiply only in living cells (unlike bacteria, viruses cannot be cultivated on dead culture media); both produce their specific effects only in definite types of cells and tissues (in animals, viruses most often affect epithelial and nervous tissue); both may have a stimulating effect on cells, as the virus that causes warts and the gene that causes neurofibromatosis (Chap 16); or a destructive effect, as the virus that causes infantile paralysis and the gene that causes muscular dystrophy (Chap. 16); and finally, both can be caused to mutate by means of X rays, and both may undergo spontaneous mutation

There are, however, some notable differences between viruses and genes. (1) In all but a few of the simplest one-celled organisms, genes are aggregated in chromosomes where they are arranged in a definite linear order, whereas viruses have no such organization. (2) Except for a brief period during mitosis, genes are retained within the nuclear membrane of the cell, while some viruses are found in the cytoplasm of the cell as well as in the nucleus, and others are found only in the cytoplasm. (3) So far as known genes ordinarily reproduce themselves only once for each cell division, whereas viruses, judged by the amount of virus obtainable from infected cells, must reproduce on a large scale. (4) Most genes in a

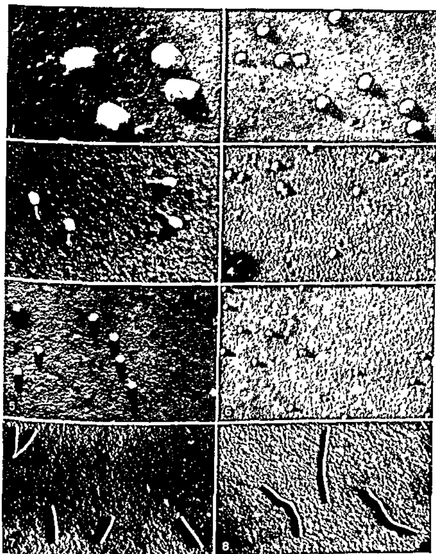
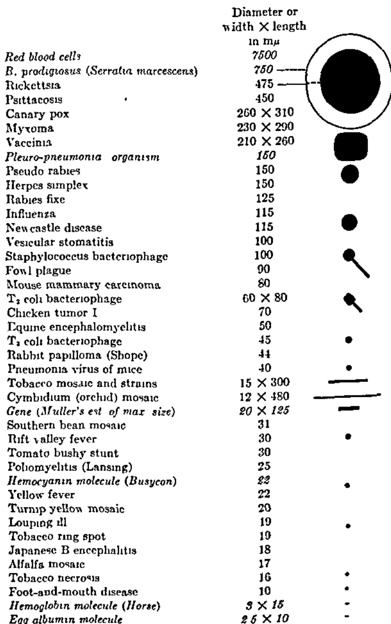


Figure 71. Electron micrographs of eight viruses shown at the same magnification (×40,000). (1) Vaccine virus (2) PR8 influenza virus (3) T_2 bacteriophage (4) Shope papilloma virus. (5) T_3 bacteriophage. (6) Bushy-stunt virus (7) Tobacco-mosaic virus (8) Cymbidium (orchid) mosaic virus. [*Courtesy of A. H. Gold and D. D. Jensen,* 1951. *Micrographs by R. C. Williams. Virus preparations by staff members, Virus Laboratory, University of California, Berkeley From Stanley, in Rivers (ed), "Viral and Rickettsial Infections of Man,"* 2d *ed , J B. Lippincott Company, aided by a grant from the National Foundation for Infantile Paralysis, Inc.*, 1952.]



	Diameter or width × length in mμ
Red blood cells	*7500*
B. prodigiosus (Serratia marcescens)	*750*
Rickettsia	475
Psittacosis	450
Canary pox	260 × 310
Myxoma	230 × 290
Vaccinia	210 × 260
Pleuro-pneumonia organism	*150*
Pseudo rabies	150
Herpes simplex	150
Rabies fixe	125
Influenza	115
Newcastle disease	115
Vesicular stomatitis	100
Staphylococcus bacteriophage	100
Fowl plague	90
Mouse mammary carcinoma	80
T_2 coli bacteriophage	60 × 80
Chicken tumor I	70
Equine encephalomyelitis	50
T_3 coli bacteriophage	45
Rabbit papilloma (Shope)	44
Pneumonia virus of mice	40
Tobacco mosaic and strains	15 × 300
Cymbidium (orchid) mosaic	12 × 480
Gene (Muller's est of max size)	*20 × 125*
Southern bean mosaic	31
Rift valley fever	30
Tomato bushy stunt	30
Poliomyelitis (Lansing)	25
Hemocyanin molecule (Busycon)	*22*
Yellow fever	22
Turnip yellow mosaic	20
Louping ill	19
Tobacco ring spot	19
Japanese B encephalitis	18
Alfalfa mosaic	17
Tobacco necrosis	16
Foot-and-mouth disease	10
Hemoglobin molecule (Horse)	*3 × 15*
Egg albumin molecule	*2.5 × 10*

Figure 72. Approximate sizes of viruses and reference materials (*From Stanley, in Rivers (ed.), "Viral and Rickettsial Infections of Man," 2d ed., J. B. Lippincott Company, aided by a grant from the National Foundation for Infantile Paralysis, Inc.,* 1952.)

given organism are distinctly beneficial and even necessary to the life of the organism as a whole (owing, no doubt, to countless generations of trial and error by mutation and selection), while most viruses so far discovered are lawless invaders which injure or kill the host, although a few (the so-called latent viruses of plants) may be carried by a healthy plant of one species to another species in which they cause disease The potato plants raised in the United States, for example, in most cases carry a virus which has no apparent effect upon the potato, but which produces disease in Turkish tobacco, as can be shown by inoculating the tobacco plant with juice from the potato plant Certain cherry trees and plum trees, although themselves healthy, carry a virus which produces disease in peach trees. Several species of lily are known to carry a virus disease of tulips. In the healthy plant they may be neither beneficial not injurious, although it is possible to imagine cases of mutual benefit (symbiosis) between a virus and the host.

There is, with respect to the effects produced, a distinct parallelism between a virus and the usual newly mutated gene in that both tend to be injurious to the cell, often in strikingly similar ways Thus if one did not know the cause of infantile paralysis and certain types of hereditary muscular atrophy, respectively, he might not be able to tell from the effects produced that the former was due to a virus and the latter to a gene; since in both diseases there is a destruction of the motor cells in the spinal cord, leading to paralysis of certain muscle groups

W. M. Stanley[1] and his coworkers have made many important discoveries regarding the structure of viruses, all of which have great interest for the student of the gene In 1935 Stanley isolated tobacco-mosaic virus in the form of needlelike crystals This material was later found to be a nucleoprotein of a molecular weight of about 40,000,000 The size of the virus particle is shown in Fig 72 Subsequently, more than a dozen viruses have been isolated, about half of them as crystals Structurally all are comparable to tobacco-mosaic virus in complexity and are composed largely of nucleoprotein. By chemical analysis 19 different amino acids, the building blocks of proteins, have been identified in tobacco-mosaic virus, and the percentage of each amino acid has been calculated Among the several distinct strains of tobacco-mosaic virus Stanley and others have found differences in amino acid composition, and most important of all, they have shown that the mutation of a virus may be accompanied by changes in the amount of one or more of the amino acids or by the introduction of an entirely new amino acid into the virus struc-

[1] W M Stanley and M A Lauffer, Physical and Chemical Procedures, in Thomas M Rivers (ed), "Viral and Rickettsial Infections of Man," 2d ed , J. B Lippincott Company, Philadelphia, 1952.

ture Small changes in chemical structure were sometimes accompanied by marked changes in virulence.

What chemical change takes place when a gene mutates? By analogy with the viruses one might expect a mutation to involve a loss, a gain, or a rearrangement of the amino acids making up the gene. Recent investigations, however, suggest that most mutations may involve a loss, a gain, or a rearrangement of nucleotides rather than amino acids. It is a well-established fact that reverse mutations are possible Cases are known in which a normal gene has mutated to some new recessive type, and later by reverse mutation the normal gene has returned This is one of the classes of facts that has led most students of mutation to the view that recessive mutations are not ordinarily losses of entire genes. Wright points out that many recessive mutations are probably inactivations of dominant genes [1] A minute loss or deletion would be transmitted in the same way as a gene change It is obvious, however, that in cases of multiple alleles, as in the albino series in the guinea pig (Chap 7), not more than one allele could be due to a total absence, because logically there can exist only one absence of the same thing. A series of alleles could of course consist of a series of losses of *parts* of the dominant gene.

HOW DO GENES ACT?

The nature of the bond that holds the genes together in linear order in the chromosome has been investigated, but is still uncertain, as is the nature of the differences among the various genes along the chromosome

One thing however seems clear· the gene has the power of taking substances from its environment and synthesizing its own likeness In addition to this property of autocatalysis, which normally may be exercised only once for each cell division, genes act directly or indirectly as catalytic agents in cell growth and cell differentiation. Without this latter property, of course, we would not know of the existence of genes

In most cases the effect of a gene on the development of a character is probably indirect, as in the case of the development of pigment in the Himalayan rabbit discussed on page 187, where an enzyme produced under the influence of the gene functions in the development of pigment

Most characters are the result of the combined action of numerous genes, and not all of these multiple genes are active at a given moment One gene may affect the production of a particular chemical substance that is prerequisite to the productive activity of a second gene, and so on in a chainlike fashion A gene can only produce its specific effect after the groundwork has been laid for it. The automatic and accurate timing

[1] Sewall Wright, Evolution in Mendelian Populations, *Genetics*, 16:97–159, 1931.

of gene action seems to be the key to the differentiation of the developing organism

A very interesting example of this chainlike process of gene action has recently been worked out in Germany and is described by the biochemist Adolph Butenandt,[1] winner of the Nobel prize in chemistry for 1939 The results were obtained with the cooperation of the biologist Alfred Kuhn, using the flour moth *Ephestia kühniella* as the experimental animal This insect normally has dark-brown eyes, due to the presence of pigment A recessive mutation *v* gives pink eyes in the adult and practically colorless eyes in the caterpillar.

It was shown that under the influence of the dominant gene v^+ the amino acid tryptophan was transformed into the amino acid kynurenine This transformation is made possible by an enzyme produced by the v^+ gene; in the presence of a double dose of the recessive gene *v* this chemical change does not take place and tryptophan accumulates in the bodies of the moths.

Two other dominant genes are required to produce the eye pigment One of these, cn^+, is needed for the production of an enzyme that converts kynurenine into hydroxykynurenine The other, wa^+, must be present for the production of a protein carrier, which is a necessary part of the pigment. A recessive mutation of either of these two genes blocks pigment formation. The steps demonstrated in this chainlike process of pigment formation are shown in the diagram (Fig 73)

The general conclusion from this case, and similar cases that have been discovered in other organisms, is that genes bring about their effects by means of specific enzymes. Butenandt, as well as most investigators in chemical genetics today, thinks it improbable that the genes themselves have an enzyme character, more likely the gene produces an enzyme or in some way controls enzyme activity.

In Drosophila, genes *v* (vermilion) and *cn* (cinnabar) behave like those just described in the flour moth Similar genes seem to be widespread in insects. In California in 1941 G W Beadle and E L Tatum, who had been working on the problem of the action of these two genes, decided to take up the study of gene action in plants They chose the red bread mold, *Neurospora crassa*. This relatively simple organism proved to be very favorable material Many other investigators have since worked with it. A readable and well-illustrated account of the experiments has been written by Dr. Beadle.[2]

[1] Adolph Butenandt, The Mode of Action of Hereditary Factors, *Endeavour*, 11:188–192, 1952

[2] G. W. Beadle, Genes and the Chemistry of the Organism, *Am Scientist*, 34:31–53, 1946

The normal Neurospora is able to live on a rather simple diet of various salts, sugar, water, and one of the B vitamins, biotin. Like plants in general it synthesizes other vital substances—certain vitamins, amino acids, and so on In general each mutation blocked the ability to produce some specific vitamin or amino acid. Consequently the mutant would grow only if it were fed this substance. From these experiments it is concluded that each normal gene has one primary effect; commonly, it seems, the primary work of a gene is the production of a specific enzyme. The

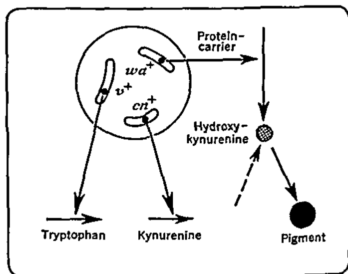


Figure 73. Diagram illustrating the action of genes v^+, cn^+, and wa^+ in a pigment-forming cell of the eye of an insect (*Courtesy of A. Kühn*)

enzyme is an essential link in the chain of synthesis of the vital substance. The lack of the vital substance may, of course, result in manifold effects in complex organisms An example of such a case in man was described on page 99 under the head of phenylketonuria, where a mutant gene blocked the formation of an enzyme, the lack of which led to many deleterious effects.

In peas and corn we have interesting examples of gene effects displayed at the chemical level. These relate to the recessive alleles for *wrinkled* in peas and *sugary* in corn. In both cases the starch grains formed in the cells of the plant are very different in appearance from the grains in round peas and starchy corn, respectively. Figure 74 shows in outline the two types of starch grains in peas, as drawn by R. P. Gregory, who first reported the existence of this difference in 1903 Its

demonstration is very simple; one needs only to mount a bit of the crushed cotyledon (preferably after soaking) in a drop of water on a microscope slide and examine under moderate power It will be noted that the grains from both varieties are variable in size, but that those from the round seeds are on the average larger and are ovoid and *simple* in outline. Those from wrinkled seeds are irregular in shape and often *compound.*

In 1908 A. B Darbishire added the interesting observation that the starch grains from a heterozygote of round and wrinkled peas are intermediate in shape: many grains are large and simple, but round instead of

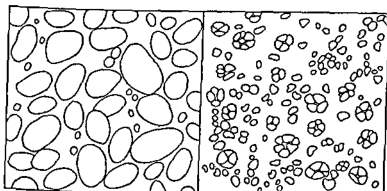


Figure 74. Outlines of starch grains in peas, showing the simple form (*left*) present in round peas and the compound grains (*right*) from wrinkled varieties Magnification the same in both figures. (*From Bateson, "Mendel's Principles of Heredity", after Gregory*)

ovoid, with a mixture of compound grains The microscope thus enables us to demonstrate lack of dominance in a case where the naked eye classes the homozygote and the heterozygote together

Figure 75 represents a comparable drawing of the starch grains in two types of corn As in peas, the variety which is smooth-seeded has the simple grains, and the one with wrinkled (sugary) seeds has the compound grains.

The starch grains in plants, of course, are derived from sugar which has been produced by photosynthesis The sugar is converted into starch under the influence of enzymes It seems probable, therefore, that the alternative genes in peas and corn act through the production of specific enzymes concerned with the formation and deposition of different kinds of carbohydrates

In the development of most characters there are probably several intervening steps between gene and character. On the other hand, the

formation of specific agglutinogens in the blood corpuscles may be the direct effect of specific genes acting within the cell during its differentiation into a corpuscle. The production of any agglutinogen ordinarily depends upon the presence of a gene that is dominant to its allele for lack of that agglutinogen. In the usual case the agglutinogen is present in at least one parent of the individual who has that agglutinogen.

The action of genes, naturally, is always dependent upon the substances which surround them in the cell and upon the physical factors,

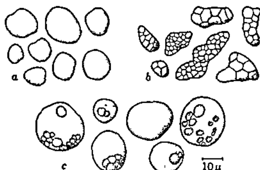


Figure 75. Starch grains in endosperm of maize 50 days after pollination. (*a*) Simple grains from starchy maize. (*b*) Compound grains from sweet maize. (*c*) Globules of liquid dextrin from sweet maize, some of which contain both simple and compound grains. *(From Sharp, "Introduction to Cytology," McGraw-Hill Book Company, Inc., after Lampe)*

such as temperature, that compose the physical environment. Hence the net result—the character—is always the product of the interaction of genes and environment This point was emphasized in Chap 11. One further illustration may be given here. Some varieties of rabbits have yellow fat and others white fat. The difference depends upon a single gene, yellow fat is recessive. The dominant gene here seems to work by conditioning the development of a specific enzyme, which changes the yellow substance xanthophyll found in green plants into a colorless substance. The recessive yellow-fatted rabbit is unable to produce the enzyme; hence the xanthophyll supplied in the green feed is stored in the fatty tissue If rabbits are deprived of green feed, both varieties will develop white fat.

POSITION EFFECTS

The genes on a chromosome are lined up in a single row. In general, they do not work as do men on an assembly line in a factory, where each

man does his part right after the man standing next to him. The position of genes along the chromosome seems to be largely a matter of chance. Their times of action do not correspond to their linear order in space. A better analogy for the genes at work would be that of a row of chemists in a laboratory. Each chemist has the job of directing some specific chemical process. The products of the labors of all the chemists are brought together at the appropriate times and places to produce the finished products of the laboratory—the characters of the organism.

This conclusion is based upon the fact that, in general, changes or reconstitutions within a chromosome, such as an end-for-end *inversion* of a section of a chromosome or a *translocation* of a piece of a chromosome to a member of another pair, seem not to alter the effects of the genes, even though in the process some genes find themselves next to new neighbors. In Drosophila, however, many exceptions to this rule have been reported—cases in which a phenotypic effect follows the change in position of a gene. Such an effect is known as the *position effect*. Apparently it has not been reported in any other animal, which may of course signify merely a lack of adequate study of other species. In plants, position effects have been described in *Oenothera blandina* and in *Zea mays*. There is still no answer to the question as to how widespread position effects may be in plants and animals. Further research is called for.

Several physiological explanations of position effects have been proposed, but so far no method has been developed for testing them. This also remains a problem for future research.

CAUSES OF MUTATIONS

If the Lamarckian theory of the inheritance of acquired characters—plausible and attractive as it is to many—must be given up as contrary to the evidence, what is there left as the cause of hereditary changes? Do mutations occur from causes residing within the organism, or are they produced by forces from without, or do both factors play parts in the process? This question appears to be an ideal one for experimental testing.

An attempt to induce mutations directly by changing the environment is not at all the same thing as an attempt to obtain a Lamarckian effect. In the Lamarckian experiments the environment or activities of the organism are first used to change some characteristic of the organism—such, for instance, as the use of ultraviolet rays to stimulate pigment formation—with the idea that the new characteristic will produce a specific change in the hereditary material of the organism. Followers of Lamarck thus assume a 1:1 relationship between the change in the bodily characteristic and the supposed change in the hereditary material. In the ex-

perimental induction of mutations, on the other hand, the environmental agent is so applied that it will reach directly the reproductive cells and there bring about a change. The contrast between the two types of experiment is shown graphically in Fig 76.

In the case represented on the left, the surface of the organism is exposed to ultraviolet rays. As a result pigment is formed near the surface, but the rays fail to reach the reproductive cells, and no mutation is induced In the case shown on the right, the rays are applied directly to the reproductive cells, with the result that mutations are induced.

In experiments on direct induction of mutations there is no assumption whatever as to the type of mutation that may result. Experience shows that the type of mutation has no direct relationship to the kind

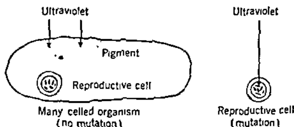


Figure 76. Diagram showing the difference between the supposed inheritance of an acquired characteristic and the direct induction of a mutation.

of environmental agent used A mutation induced by ultraviolet rays may have nothing whatever to do with pigment formation

A wide variety of chemical and physical agents have been used in the attempt to induce mutations. Among these are alcohol, lead, arsenic, ammonia, iodine, manganese, acids, alkalis, alkaloids, neutral salts, 2,4-D, ether and other anesthetics, foreign proteins, antibodies, lack of oxygen, centrifugal force, supersonic vibrations, high temperatures, low temperatures, X rays, radium, neutrons, carcinogenic chemicals, and mustard gas and related compounds The list is not complete.

Most of the agents listed are distinctly poisonous or injurious to living cells and produce permanent changes when applied in the proper concentrations. Positive effects upon the offspring of treated plants and animals, however, have been demonstrated with only a few of the agents used. Aside from radiations, high and low temperatures, and a number of organic chemicals, not one has yielded a satisfactory series of gene mutations in the hands of a number of investigators. Individual successes have been claimed for many of the agents listed, but unless an experiment can be successfully repeated by other competent workers, there is

always grave doubt as to the adequacy of control or technique It is true that no amount of negative evidence is sufficient to prove a universal negative, and there is always the possibility that some experimenter may hit upon a new method which will yield positive results This is strikingly illustrated in the case of X rays and certain chemicals mentioned later

Mutations from X Rays and Other Short-wave Radiations

Prior to 1927 numerous experimenters had used X rays in an attempt to produce mutations in insects and mammals Most of the experiments



Figure 77. H. J Muller, 1890– .

gave negative results, although in a few cases there were strong suggestions of positive results A satisfactory demonstration of the induction of mutations by means of X rays had not been accomplished

In 1927 Professor H. J. Muller, at that time of the University of Texas, announced that by the use of special methods which he had developed

over a period of years for the detection of spontaneous mutations (mutations in untreated animals), he had at last been able to demonstrate the induction of true gene mutations by means of X rays For this and other important investigations in genetics Professor Muller, now at Indiana University, was awarded the Nobel prize in medicine for 1946 He used the fruit fly Drosophila and obtained mutations in a high proportion of the sperms and eggs of treated flies Comparison of the mutation rates in treated and untreated flies showed that heavy X-ray treatment had caused a 150-fold increase in the mutation rate over that in the untreated flies

The mutations were for the most part similar to or repetitions of those that had been previously observed in untreated flies, although some were different Lethal mutations greatly outnumbered those with visible effects Dominant lethals were about as numerous as recessive lethals. The great majority of the visible mutations were recessive, just as they are in untreated flies Chromosome breakages and chromosome rearrangements also were frequent

In his Nobel-prize lecture, almost twenty years later, Muller stated:[1]

> Now it is found in *Drosophila* that the radiation-induced mutations of the genes (we exclude here the demonstrable chromosome rearrangements) are in every respect which has been investigated of the same essential nature as those arising naturally in the laboratory or field. They usually occur in one gene without affecting an identical one nearby They are distributed similarly in the chromosomes The effects, similarly, may be large or small and there is a similar ratio of fully lethal to so-called visible gene mutations.

At about the same time as Muller's original work, L. J. Stadler, of the University of Missouri, independently obtained positive results with barley and corn. During the next few years numerous investigators abundantly confirmed the positive effects of X rays. Radium was found to give the same results as X rays, and the frequency of mutation was found to vary directly with the dosage

This direct relationship between the quantity of the penetrating radiation and the frequency of induced mutations is supported by many later experiments In general, a given dose administered within a short period of time has the same effect as the same dose spread over a longer period This rule seems to hold at least up to a certain intensity; beyond a certain point the law of diminishing returns may apply. Muller considers that no dose is too small to give a mutation. He thinks that "each individual ionization, and probably even each activitation of an atom, carries its definite chance of producing a mutation."[2]

[1] H. J Muller, The Production of Mutations, *J. Heredity*, 38:259-270, 1947.

[2] H. J. Muller, Radiation Damage to the Genetic Material, *Am Scientist*, 38:33-59, 399-425, 1950.

Mutations have been induced in viruses, in many species of plants ranging in complexity from bacteria to seed plants, and in animals ranging from one-celled species to mammals Some practical applications have been made of the technique An X-rayed strain of *Penicillium* gave a mutant that produced more than double the amount of penicillin Superior varieties of barley and wheat have been produced by X rays In recent years seeds of barley, wheat, and oats have been exposed to the intense radiations from atomic-bomb explosions. It was no surprise that mutations were induced comparable to those from heavy exposure to X rays As usual, most of the mutations were distinctly deleterious Other short-wave radiations such as gamma rays, electrons, protons, alpha particles, and neutrons have all given positive results

The earlier experiments in which sizable organisms were treated with ultraviolet rays gave negative results, owing to the low penetrating power of ultraviolet rays. Later, when insect eggs, the pollen from plants, or bacteria were irradiated, mutations were produced Visible light has no mutagenic effect

Whatever the cause, mutations are all alike in one respect each is an isolated event arising practically always in a single chromosome of a pair, hence appearing first in the heterozygous state Mutations may occur at any point in the life cycle, either in somatic cells or in germ cells An example of somatic mutation is a bud mutation on a fruit tree Such a mutant may be propagated by cuttings Fruit borne by that bud or any branch from that bud will possess the mutant in all its cells Only those mutations that are found in the germ-cell line are transmitted sexually in the gametes

Naturally we are most interested in the effects of X rays and other penetrating radiations on human beings, especially so since the discovery of atomic fission and its applications in warfare and industry Experiments on mammals are therefore of particular interest

At about the time of Muller's initial success in inducing mutations in Drosophila with X rays, experiments were performed with X rays on mice by several independent investigators, the results were inconclusive Shortly thereafter in a well-controlled experiment with a highly inbred and homogeneous strain of guinea pigs (Figs 85 and 86) H H. Strandskov,[1] of the University of Chicago, treated males by exposing the testes to heavy doses of X rays sufficient to bring about atrophy of the testes and temporary sterility Seventy-one treated males produced 173 offspring, conceived before the onset of sterility or after recovery of fertility. There were no visible mutations among these 173 offspring of treated males, nor among the 238 offspring in the second generation, nor the 185

[1] H H Strandskov, Effects of X-rays in an Inbred Strain of Guinea-pigs, *J. Expt Zool*, 63:175–202, 1932.

in the third generation. The controls produced on the average 2.69 offspring per litter as compared with 2.04 from the treated males. This decrease was attributed to the production of dominant lethal effects, either chromosome changes or gene mutations.

In one of the latest of numerous similar experiments performed with mice during the past twenty years Kalmus[1] et al., of McGill University, Montreal, used X rays on males of a highly inbred (hence homogeneous) strain. The average size of litter from untreated males was 7.65, and from treated males 5.95. Thus the effect of reduction in size of litter was very similar to that in Strandskov's experiment with guinea pigs.

An excellent critical review of induced genetic changes in mice is given by Dr. Hans Gruneberg,[2] of University College, London, in his recent comprehensive work "The Genetics of the Mouse." He concludes that the mouse, like all other species of animals and plants so far studied, is susceptible to short-wave radiations.

In most of the experiments carried out in this country, in England, and in Germany males rather than females have been irradiated. Repeatedly it has been found that litters sired by treated males mated to untreated females are reduced in size. Studies show that many embryos from such matings die in very early embryonic stages and are absorbed *in utero*. The principal cause of such deaths is thought to be gross chromosome changes rather than gene mutations.

A particular type of chromosome change known as a *reciprocal translocation* occurs frequently. This results in semisterility of the mouse that carries it. A reciprocal translocation is brought about through two simultaneous breaks in two chromosomes of different pairs (nonhomologous chromosomes) in a single cell, followed by the exchange of pieces of the broken chromosomes (Fig. 78).

If such a translocation occurs in a gamete it may appear in the heterozygous state in an F_1. Such a heterozygous animal is phenotypically normal (in the absence of a position effect), since it has the normal complement of genes. New linkage relationships, of course, result from the translocation.

Some of the gametes produced by an individual carrying a translocation are abnormal in that they lack certain genes and carry duplicates of others, as shown in Fig. 78. Zygotes formed from such abnormal gametes likewise are unbalanced in their gene constitution, and these usually die in early embryonic stages. The lethal effect of such an abnormal gene make-up is dominant. Approximately half of the living offspring of a

[1] H. Kalmus, J. D. Metrakos, and M. Silverberg, Sex Ratio of Offspring from Irradiated Male Mice, *Science*, **116**: 274–275, 1952.

[2] Hans Grüneberg, "The Genetics of the Mouse," 2d ed., Martinus Nijhoff, The Hague, 1952 (also published as vol. 15 of *Bibliographia Genet.*)

semisterile parent are perfectly normal both phenotypically and genetically, half are semisterile Semisterility is thus transmitted as though it were due to a dominant gene

G D. Snell, of Jackson Memorial Laboratory, Bar Harbor, Maine, was the first to suggest that semisterility in mammals, following radiation,

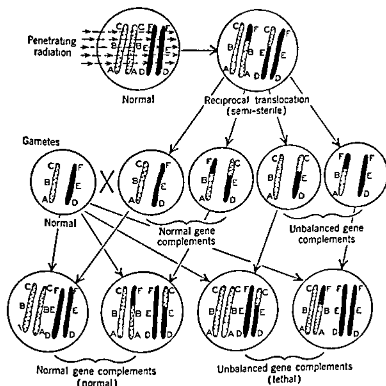


Figure 78. Diagram illustrating the production of a reciprocal translocation, with consequent semisterility.

was due to reciprocal translocation. Confirmation has come from cytological and genetical studies. A similar condition was well known in Drosophila when Snell wrote.

As to visible mutations induced by radiation, Paula Hertwig in Germany has described four separate recessive mutations found in the descendants of purebred mice exposed to X rays Males were irradiated. Their sons were then backcrossed to at least four, but usually to from seven to nine of their daughters. Any son that received a recessive gene from his treated father should pass it on to half of his daughters. One-fourth of the offspring of a carrier daughter mated to her father should

show the recessive trait. It was in the offspring of these backcross matings that the mutants showed up.

These four mutated genes are listed in Gruneberg's table of Mendelian traits in mice (Chap. 19). Two of them, designated *Kreisler* (*kr*) and *shaker with syndactylism* (*sy*) were obtained from males sired prior to the onset of sterility in their fathers The other two, *anemia* (*an*) and *oligodactylism* (*o*) came from males sired following a period of temporary sterility in their fathers The first two mutations therefore are regarded as having been induced in mature sperms and the last two in spermatogonia The four mutants are all specific abnormal types involving either the skeletal, nervous, or circulatory system

W L Russell,[1] of Oak Ridge National Laboratory, has been most successful in producing mutations in mice He exposed wild-type males to a single dose of X rays and mated these to females homozygous for seven well-known autosomal recessive genes a, non-agouti, b, brown; c^{ch}, chinchilla, p, pink-eyed dilution; d, maltese, se, short ear; and s, piebald The genes c^{ch} and p are linked, as are the genes d and se The treated males were of constitution AA BB $(C\ P)(C\ P)$ $(D\ Se)(D\ Se)$ SS. The offspring from such matings in the absence of mutation would thus be Aa Bb $(C\ P)(c^{ch}\ p)$ $(D\ Se)(d\ se)$ Ss. Mutation of any one of the seven dominant genes, such as a mutation of A to a, could be detected in the offspring of the treated male

As controls, unexposed wild-type animals were mated to the multiple-recessive stock With the dosage used (600 roentgens of X rays) sterility began a few weeks after irradiation. Following recovery from the temporary sterility, matings were made Among 48,007 offspring from treated males 53 mutations were found at the seven previously mentioned loci Mutation was much more frequent at some loci than at others· there were 11 mutations at b, 3 at c, 6 at d, 8 at p, 25 at s, and none at a and se Some of the mutations were identical to the recessive alleles of the females, some were different

Among the 37,868 untreated controls only two mutations occurred, one of these was at locus d, the other at locus s.

Besides examining carefully the offspring of controls and treated males for mutations at the seven specific loci, Russell made a cursory examination for dominant visible mutations at any locus Six such dominant mutations were found among the offspring of irradiated males and none among the controls.

The great difference in mutation rate between the irradiated and the control animals in this extensive experiment is convincing proof that X rays cause mutations in mammals

[1] W. L. Russell, X-ray Induced Mutations in Mice, *Cold Spring Harbor Symposia Quant. Biol*, **16**:327–335, 1951.

Chemical Induction of Mutations

Many chemical substances have been used in attempts to produce mutations in plants and animals Some of the experiments were done before Muller's success with X rays and some thereafter Numerous positive results have been claimed. The most recent and best-controlled experiments, however, prior to the Second World War failed to verify earlier claims Two of these,[1,2] in which results were negative, involved substances to which man is repeatedly exposed—lead and alcohol Reviews of earlier experiments in which positive results were claimed will be found in these papers. In his book "The Genetics of the Mouse," previously cited, Grüneberg reviews the later experiments with alcohol administered to mice and finds no evidence of a mutagenic effect of alcohol

Mustard Gas. The first unquestioned and repeatable positive results with chemicals were obtained in Scotland during the Second World War Charlotte Auerbach,[3] of the Institute of Animal Genetics, the University of Edinburgh, one of the investigators who carried out the experiments, gives a brief history of this important advance·

> At the beginning of the war, Dr J M Robson who then was engaged in a pharmacological study of war gases, drew my attention to the similarity of mustard gas burns and X-ray burns Both heal only with difficulty and, when healed, have a tendency to break down again Dr Robson had also obtained some direct evidence for an inhibitory action of mustard gas on mitosis He thought of the possibility that it might affect the chromosomes in a similar way to X-rays We decided to test this possibility on *Drosophila*
>
> From the very first, our attempts were successful In *Drosophila* also, mustard gas proved a very effective mitotic poison Treatment of males and females led to more or less severe sterility This could be shown to be due partly to inhibition of cell division in the gonads, partly to death of zygotes from treated gametes Early in 1941 we carried out a first test for sex-linked lethals. The result left no doubt about the mutagenic ability of mustard gas 7% sex-linked lethals were obtained in about 1300 treated chromosomes, the controls had a mutation rate of about 0 2% Among the induced lethals, a few could be shown to be connected with large rearrangements, and many with small deficiencies The cytological evidence was obtained by Dr and Mrs Slizynski In subsequent tests with higher doses, it was possible to induce much higher mutation rates

[1] E C. Cohn, A Comparison of the Descendants of Lead-poisoned Male Guinea Pigs with Those from Untreated Animals of the Same Closely Inbred Strains, *J. Expt. Zool*, 60:427–484, 1931 (So far as known this is the latest experiment of this sort with lead)

[2] F. M Durham and H M Woods, Alcohol and Inheritance: An Experimental Study, *Med Research Council (Brit) Spec. Rept Ser*, No. 168, 1932

[3] Charlotte Auerbach, Chemical Induction of Mutations, *Proc 8th Intern Congr. Genet*, 1948 (*Hereditas* suppl. vol.), Berlingska Boktryckeriet, Lund, 1949.

The same types of effects were produced by mustard gas as by X rays, and on a comparable scale These effects include visible mutations, dominant and recessive lethals, both sex-linked and autosomal, semilethals, "detrimentals" (mildly injurious), and chromosome changes

Related compounds belonging to the general group of "mustards" proved effective agents, while equally poisonous and penetrating substances—lewisite, osmic acid, and picric acid—were not effective.

The mutagenic properties of mustards have been confirmed by a number of independent workers with organisms as diverse as bacteria, molds (Neurospora and *Penicillium*), seed plants (barley, corn, and *Tradescantia*), several species of insects, and perhaps mice

A number of other chemicals have since given evidence of mutagenic properties Formaldehyde added to the culture medium has produced mutations in Drosophila Various cancer-inducing substances have proved effective, this has revived interest in the possibility that certain types of cancer are the result of somatic mutation.

Natural organic peroxides seem to induce mutations, as do certain substances that have previously been irradiated with ultraviolet

Low oxygen pressure causes a great reduction in mutation rate

THE CAUSES OF NATURAL MUTATIONS

In his classical work on "The Origin of Species" Darwin uses the term *mutation* in the sense of transformation of a species into something different, largely through the "accumulation of numerous, slight, spontaneous variations" Since the time of De Vries, usage has decreed that mutation refers to a single, sudden hereditary change, the changed individual being known as a *mutant.*

As instances of spontaneous variations Darwin mentions, under the head of bud variations, the appearance of a moss rose on a common rose, or a nectarine on a peach tree Incidentally, we now know that the smooth skin of the nectarine is due to a recessive mutation; the downy skin of the peach is dominant. Darwin had no theory as to the causes of spontaneous variations, although he thought that the nature of the environmental conditions "apparently plays a quite subordinate part" We have not yet gone far from this view in our search for the causes of spontaneous or natural mutations, whether the result of gene changes or chromosome changes.

Undoubtedly some spontaneous mutations are induced by natural radiations emanating from radioactive substances in the rocks, soil, water, or atmosphere of the earth, from the body of the organism itself, or from ultraviolet rays and cosmic rays arriving from outer space All organisms on earth are exposed to such radiations. The proportion of spontaneous

mutations so induced is unknown Calculations by Muller and others, however, show that the measured intensity of natural radiation is wholly inadequate to account for the observed rate of spontaneous mutation in Drosophila. These calculations are based upon the assumption that the rate of mutation is proportional to the dosage at the low intensities of natural radiations, just as it is at the higher intensities used in experiments

Since the recent discovery of chemical mutagenic agents it seems probable that some spontaneous mutations are due to the chemical environment, including substances taken in as food The rate of spontaneous mutation is known to increase with rise in temperature, so do ordinary chemical processes increase in rate with rise in temperature. The suggestion has been made that a change in a gene constituting a mutation may occur as an incidental result of the metabolism of the cell, perhaps through the occasional failure of a gene to duplicate itself with perfect accuracy during cell division Such a slip would be expected more often at higher temperatures. So far these are only speculations The mechanism of gene duplication is still unknown The nature of the chemical change that gives rise to a mutation is also unknown.

THE CONTROL OF MUTATIONS

The induction of mutations by radiations or chemicals has been compared to firing a gun at a target in the dark. In both cases the chance of making a hit is small If the hit occurs, there is no predicting what the effect will be, though it is most likely to be harmful

In using radiations or chemicals—even the strongest dosage that can be used without killing the organism—the great majority of the genes seem to escape being struck The occasional hits result in mutations of the same types as occur naturally But precisely what these mutations will be cannot be predicted There is as yet no way of producing a desired mutation to order, and any artificial induction of mutations is sure to produce a great majority of undesirable ones

In one respect, however, the results are predictable· experience teaches that certain mutations occur again and again, and some with greater frequency than others This means that some genes are more stable than others Furthermore, there is a limit to the variety of possible mutations —a limit set by the nature of the organism itself. For example, among the millions of Drosophila that have been bred in experiments during the past decades, dozens of mutations have occurred changing the normal red eye color to darker shades, such as purple or brown, or to lighter shades, grading down to white. Most of these mutations have occurred again and again, but a mutation causing the eyes of Drosophila to become green has never been observed, notwithstanding that green is the normal

eye color of some other insects, for example, certain mosquitoes and dragonflies This means that the nature of Drosophila sets a limit to the kinds of mutations that can take place in the animal

Similarly, in man and many other mammals numerous mutations have occurred affecting hair color, but the color is always black or white or some shade of brown or red—never green. Evidently something in the chemical nature of the organism limits the possible color mutations.

CHROMOSOME CHANGES

Under this head are included all changes in the normal number of chromosomes, additions and losses of parts of chromosomes, changes in the arrangement of genes along the chromosomes, and in fact all gross changes that are visible under the microscope. The genes themselves are not affected.

Polyploidy in Plants

Polyploidy refers to any increase in number of sets of homologous chromosomes beyond the diploid number. Experiments have shown several methods of inducing chromosome doubling The most striking results have been obtained with a drug known as colchicine (kŏl′-chĭ-sēn). This chemical ($C_{22}H_{25}O_6N$) is an extremely interesting substance. It is classed as an alkaloid poison and is extracted from the seeds of a plant known as meadow saffron Incidentally, it is one of the drugs used as a remedy for arthritis in man

In 1937 several European investigators and two groups[1] of American investigators working independently found that colchicine was almost a specific for the induction of chromosome doubling without cell division in plants When growing tips or buds of plants were wet with a weak solution of the drug, say 1 per cent, cells were formed with double the normal chromosome number. Frequently there was a redoubling, occasionally as many as three times. What happens in these experiments is that the normal functioning of the mitotic spindle is prevented Hence cell division is inhibited, while chromosome doubling goes on as usual. After the effect of the drug has abated, the cells with doubled chromosome numbers divide normally, and from the tissues so produced seeds and embryos with double chromosome numbers develop. There is thus a permanent change in the plant, just as there is in wild plants as a result of doubling from unknown causes All such cases in which closely related organisms show a series of chromosome numbers that are multiples of a

[1] A. F. Blakeslee and Amos G. Avery, Methods of Inducing Doubling of Chromosomes in Plants by Treatment with Colchicine, *J. Heredity*, 28:392–411, 1937, B. R. Nebel and M. L. Ruttle, The Cytological and Genetical Significance of Colchicine, *J. Heredity*, 29:2–9, 1938.

basic number are examples of *polyploidy* (*poly*, many; *ploid*, fold). An organism with a single complete set of chromosomes, like the male honeybee and numerous plants, is a *haploid* (*haploos*, single) and contains the basic number (n) of chromosomes Most sexually reproducing organisms have a double set of chromosomes and are known as *diploids* ($2n$) A doubling of a diploid set results in a *tetraploid* (*tetra*, four)

Several other drugs have more recently been found effective in inducing polyploids, while similar results have been obtained in plants—though in a much smaller percentage of treated individuals—by the use of X rays, high temperatures, low temperatures,[1] centrifuging, and by merely cutting off the end of the growing tip A number of experimenters have shown that if the growing tip of a tomato plant is cut off, thereby inducing the formation of irregular shoots under the scar tissue that is formed, some of these shoots have 48 chromosomes instead of the normal 24. Subsequent cell division was normal, so that all the cells on the tetraploid branch, including the flowers, have the doubled chromosome number. Eggs and sperms produced by such branches have twice the number of chromosomes possessed by eggs and sperms in the original plant If self-fertilization occurs, the double condition is thus perpetuated

The ease with which a great variety of plants may be artificially induced to double their chromosome number explains perhaps why the process is so common in nature. One leading investigator, Muntzing, of the University of Lund, Sweden, concludes that more than half the species of flowering plants (including many of our economically useful plants) in which the chromosome number is known are polyploids For example, in wheat and barley, species are known with 14, 28, and 42 chromosomes; in chrysanthemums, species with 18, 36, 54, 72, and 90, and in *Solanum*, which includes the potato, species with 24, 36, 48, 60, 72, and 96 chromosomes. The regularity of these series of numbers, consisting as they do of simple multiples of some lower number, clearly indicates the origin of new species from other species by polyploidy. Whether the chromosome doubling in series like those above arose within a single species or was the result of the crossing of two related species is often difficult to decide. Both types of polyploidy are known to be of frequent occurrence in plants. The second type, known as amphidiploids, is considered in Chap 14.

A typical example of a spontaneous tetraploid in plants was reported by Bamford and Winkler [2] As shown in their excellent illustration (Fig 79) the stems, flowers, leaves, stomata, and even the pollen grains, are

[1] Haig Dermen, A Cytological Analysis of Polyploidy Induced by Colchicine and by Extremes of Temperature, *J Heredity*, 29:201–220, 1938.

[2] Ronald Bamford and F. B. Winkler, A Spontaneous Tetraploid Snapdragon, *J. Heredity*, 32:278, 1941.

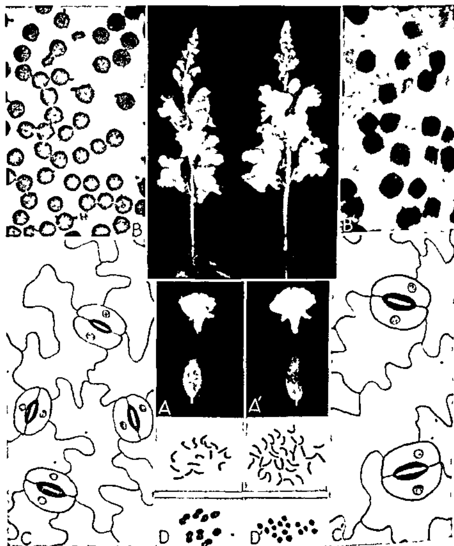


Figure 79. A spontaneous tetraploid snapdragon (right half of the figure) in comparison with a diploid (on the left) Structures in the tetraploid (A'-C') are larger than in the diploid (A-C) (A,A') Plants (B,B') Pollen. (C,C') Stomata. (D,D') Chromosomes (*From Bamford and Winkler, A Spontaneous Tetraploid Snapdragon, J Heredity, August, 1941*)

larger in the tetraploid than in the diploid plant. The authors mention the fact that tetraploid snapdragons had previously been induced by colchicine treatment by Nebel and Ruttle (see footnote, page 236) and that such tetraploids were similar to the spontaneous one.

Plants that have doubled their own chromosome make-up are known as *autotetraploids*. They often differ in many ways from diploids. they

are usually larger, have thicker stems, thicker and relatively broader leaves, and a darker green color The flowers, fruits, and seeds also are usually larger. The differences, however, are largely quantitative and are not usually such as to cause taxonomists to class the diploids and the tetraploids as distinct species Sometimes, in fact, there are no visible external differences between the two; for example, in this country in a species of spiderwort (*Tradescantia*) there are diploid and autotetraploid races growing side by side which can only be distinguished by their chromosome numbers [1]

Tetraploids develop more slowly, take longer to reach maturity, and are often hardier than diploids Tetraploid tomatoes have been found to contain about double the usual concentration of vitamin C,[2] tetraploid yellow corn has been found to have 43 per cent more vitamin A than diploid corn, and tetraploid tobacco has nearly twice as much nicotine as diploid tobacco. Tetraploid ornamental flowers of superior types have been obtained. Many choice varieties of fruits—grapes, apples, etc — are tetraploids. Muntzing[3] describes the recent development in Sweden of superior polyploids among the cereals a tetraploid rye with superior baking qualities has been developed and released to the farmers for planting.

Polyploidy in Animals

In animals, in contrast to plants, polyploidy is relatively rare, and few polyploid animals have been produced experimentally In only a few phyla of animals do the chromosome numbers suggest polyploid series; the polyploid species that do exist are usually hermaphroditic or parthenogenetic. Polyploids are known in the protozoa, flatworms, annelids, mollusks, and arthropods; and in these phyla hermaphroditism or parthenogenesis, or both, are fairly common. However, the great majority of animals are bisexual, which fact is given as one of the chief reasons for the rarity of polyploids in the animal kingdom.

In a recent interesting study of the chromosomes in earthworms, Muldal[4] investigated 23 species in five genera of Lumbricidae He found that 6 of the 23 were parthenogenetic and "almost certainly polyploid." Their chromosome numbers are 48, 54, 68, 72, 72, and 190±. The first two he considers triploids, the next three tetraploids, and the last a

[1] Jens Clausen, David D Keck, and William M. Hiesey, Experimental Studies of the Nature of Species. II Plant Evolution through Amphiploidy and Autoploidy with Examples from the Madiinae, *Carnegie Inst Wash. Publ.* 564, 1945

[2] F. W. Sansome and S S. Zilva, Polyploidy and Vitamin C, *Biochem. J. (London)*, 27:1935–1941, 1933.

[3] Arne Müntzing, Genetics and Plant Breeding, in L. C. Dunn (ed), "Genetics in the 20th Century," The Macmillan Company, New York, 1951

[4] Sylfest Muldal, The Chromosomes of the Earthworms. 1 The evolution of polyploidy, *Heredity*, 6 :56–76, 1952

decaploid. These, he finds, are all successful and widespread species Muldal points out that "parthenogenesis is important as it makes the retention of polyploidy possible, and also favors the spread of polyploid forms into new areas, since even a single parthenogenetic individual may establish a population there."

Muldal's studies have been confirmed and extended by Omodeo.[1]

That polyploid individuals do appear spontaneously in bisexual animals with fair frequency is evident, however. Fankhauser[2] of Princeton University during a period of four years examined 1,302 larvae of the newt *Triturus viridescens* raised in his laboratory. About 2 per cent of the individuals were found to be polyploids. Among these were 17 triploids, 1 tetraploid, 4 pentaploids; there was also 1 haploid.

Among the arthropods, which characteristically are bisexual, polyploid races and species are found living successfully in nature in a few groups In most cases the polyploids are parthenogenetic. A crustacean known as the brine shrimp (*Artemia salina*) is represented by a diploid bisexual form and by parthenogenetic tetraploid, octoploid, and decaploid races The polyploid races are larger than the diploids, and development is more rapid

A similar case is that of the sow bug *Trichoniscus elisabethae*, likewise a crustacean· in the south of Europe diploid races occur, with the sexes in equal numbers; in northern Europe these races are replaced by a parthenogenetic triploid race, in which males are practically absent. The eggs of the parthenogenetic race lack a reduction division and develop without fertilization

In several groups of insects polyploidy has been described. A tetraploid race of the moth *Solenobia triquetrella* ranges widely in central Europe Females only are found, and reproduction is parthenogenetic. It is probable that this race was derived from a diploid bisexual race which occupies a restricted region in Germany.

Another group of polyploid insects are members of a family of beetles known as weevils (*Curculionidae*), in which at least 17 parthenogenetic species and races have been reported One of these is diploid, eleven are triploid, four are tetraploid, and one is pentaploid. In all of them, females alone exist; the eggs develop without fertilization after a single meiotic division. In the same group, bisexual diploid species are found; in these, maturation of the gametes is normal.[3]

In the Orthoptera, a long-horned grasshopper of Europe (*Sagapedo*) is tetraploid, with 68 chromosomes. Only females exist. It reproduces par-

[1] Pietro Omodeo, Cariologia di Lumbricidae, *Caryologia*, 4:173–275, 1952 (abstracted in *Biol. Abstr.*, 27:287, 1953)

[2] Gerhard Fankhauser, Induction of Polyploidy in Animals by Extremes of Temperature, in "Biological Symposia," The Ronald Press Company, New York, 1942.

[3] Esko Suomalainen, Parthenogenesis in Animals, in M. Demerec (ed.), "Advances in Genetics," vol. 5, Academic Press, Inc., New York, 1950

thenogenetically. Two other species of this genus are bisexual, with 32 and 34 chromosomes, respectively, in the females.

Examples of polyploidy as a result of the crossing of two distinct species, which seems to be especially important in the origin of species in plants, will be described in Chap 14

CHROMOSOME REARRANGEMENTS· LOCATING THE GENE

As we have seen, the evidence from crossing over (Chap 8) indicates that the genes lie on the chromosome, arranged in a definite linear order

Figure 80. Photomicrograph of chromosomes from a cell of the salivary gland of *Drosophila melanogaster*, showing the distinctive pattern of alternating dark and light bands (*General Biological Supply House, Chicago*)

from one end to the other. This evidence, however, is indirect What is the direct evidence for such an arrangement?

In many species, including Drosophila, the chromosomes show up under the microscope as a series of granules or bands of varying sizes, resembling beads strung on a string (Fig 80). The pattern of these gran-

ules and bands in a given chromosome shows great constancy throughout the species, and during synapsis of homologous chromosomes preceding meiosis there is specific pairing of the bands and granules The natural conclusion is that these particles represent the genes What is needed, however, is the simultaneous study of the chromosome structure and the breeding results, in order to identify positively distinct structures along the chromosome as particular genes. In 1933, Professor T. S. Painter, of the University of Texas, made it possible to do this when he published the first of a series of articles announcing the development of a new technique in the study of chromosomes

The essentials of the method, as well as the early discoveries made under it, were summarized by Painter in 1934.[1] In this paper he comments that ever since the formulation of the chromosome theory of heredity cytologists and geneticists had dreamed of the day when someone would find an organism in which the chromosomes were so large that it would be possible to see qualitative differences along their length corresponding to the different genes known to reside there.

Recalling that in various species of flies, including Drosophila, the cells of the salivary glands of the larvae contained unusually large chromosomes, and that the chromosomes showed conspicuous bands or disks of deeply staining material, alternating with clearer regions, Painter began the reexamination of the salivary-gland chromosomes in Drosophila He developed an improved technique for spreading out the coiled chromosomes so that they might be more easily studied. From his own observations he gave the following description:

> The chromosome consists of an elongated more or less cylindrical rod made up of lightly staining material, while running apparently across each may be seen a great variety of "bands," some broad and deeply staining, others narrow or made up of a series of dots. A study was begun at once to determine if the patterns of bands and lines, which are so conspicuous, were constant morphological characteristics of a given element. It turned out that the landmarks are constant to a most extraordinary degree so that we were able to recognize the same element in the nuclei of different individuals and ultimately to follow any characteristic bit of a chromosome as it is shifted here and there to other chromosomes through the agency of irradiation.

A drawing of a pair of the tiny dotlike chromosomes from Drosophila, made by Bridges,[2] is shown in Fig. 81.

In order to represent the other three chromosomes on the same scale (as is done by both Bridges and Painter), a page several times the width

[1] T. S. Painter, Salivary Chromosomes and the Attack on the Gene, *J. Heredity*, **25**:464–476, 1934

[2] C B. Bridges, Salivary Chromosome Maps with a Key to the Banding of the Chromosomes of *Drosophila melanogaster*, *J. Heredity*, **26**:60–64, 1935

of this one would be needed. The same wealth of detail is found in the other chromosomes

In the salivary glands, the chromosomes remain in an elongated condition; the chromosome shown in Figs 80 and 81 are nearly a hundred times as long as the corresponding chromosome in the contracted state of an ordinary cell, as drawn in the upper right of Fig 81. Note that the

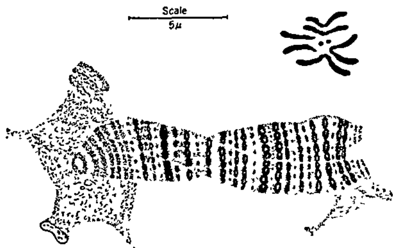


Figure 81. Drawings of chromosomes of the fruit fly, *Drosophila melanogaster* *Upper right* As they appear in pairs in the ovaries before the reduction division *Below*· On the same scale, the pair of dotlike chromosomes as they appear in the salivary glands of the larva. Scale, 5μ = 1/5,000 inch (*From Bridges, J Heredity.*)

members of the pair of salivary-gland chromosomes lie side by side, slightly twisted about one another. Somatic synapsis, as shown here, is the rule in salivary-gland chromosomes The identity of structure of the two mates is striking From end to end Bridges counted 34 separate bands on this one tiny chromosome

More recently, Slizynski,[1] of the University of Edinburgh, has studied the same chromosome in Drosophila By making use of especially favorable preparations in which the chromosomes were well stretched he was able to identify 137 bands (Fig 82). His drawing shows the elaborate method that has been devised for the identification of the bands and for relating these to particular genes The symbols for about a dozen genes are shown above the heavy horizontal line in the figure

A gene mutation produces no visible change in the bands. Gross chromosome changes, however, can be identified by the altered pattern of the

[1] B M Slizynski, A Revised Map of Salivary Gland Chromosome 4 of *Drosophila melanogaster*, *J. Heredity*, 35:323–324, 1944.

bands. There are four common types of such chromosome changes: (1) *deficiency*, a loss of one or more bands, (2) *duplication* of one or more bands; (3) *translocation*, a shifting of a piece of a chromosome to a member of another pair, and (4) *inversion*, an end-for-end reversal of a piece. All these changes occur occasionally in untreated animals; they can also be readily induced by penetrating radiation and by chemical treatment Such chromosome changes often produce phenotypic effects and may undergo Mendelian segregation. They are thus not easy to distinguish

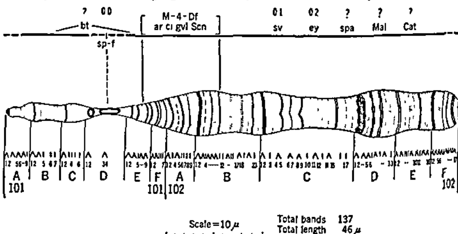


Figure 82. Drawing of salivary gland chromosome IV of *Drosophila melanogaster*, with a map above the chromosome indicating the position of the better-known genes. (*From Slizynski, A Revised Map of Salivary Gland Chromosome 4 of Drosophila Melanogaster, J Heredity, November, 1944.*)

from gene mutations The distinction can be made, however, by microscopic study of the banding pattern.

The study of chromosome changes under the microscope, in connection with the breeding results from flies showing such chromosome changes, gives the most convincing evidence of the location of the genes The two lines of independent facts thus obtained are in perfect agreement with one another, and both support the theory of the linear arrangement of the genes along the chromosome Moreover, the combination of breeding experiments and microscopic studies points to an arrangement of the genes in the chromosomes of the reproductive cells that is identical with that in the cells of the salivary glands.

We have already seen that mitotic cell division during the development of the organism ensures that all cells of the body shall have identical chromosome sets—the occasional exceptions to this rule seem to have no great practical importance. Additional evidence of this identity is supplied by the discovery that certain cells of other tissues in Drosophila and other species of flies have large banded chromosomes that

are identical with those of the salivary glands Pavan and Breuer[1] have published a very interesting paper on the banded chromosomes of a species of fly in Brazil. Their photographs and drawings (Fig 83) show identical chromosome patterns in the cells of the salivary glands and the Malpighian tubules They also found that the seminal vesicles contained cells in which the same banding pattern was present.

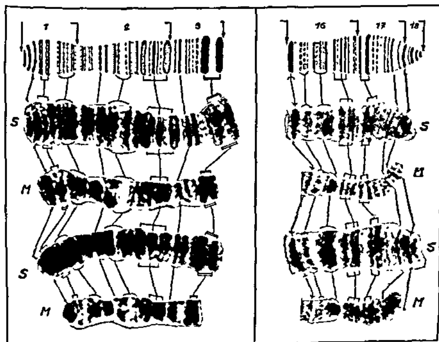


Figure 83. Drawings and photomicrographs of sections 1 to 3 (distal end of left arm) and sections 16 to 18 (distal end of right arm) of chromosome A of the fly *Rhynchosciara angelae*· chromosomes from salivary gland cells (*S*), Malpighian tubule cells (*M*). The connecting lines show the main landmarks, which can readily be identified. (*Courtesy of C Pavan and M E Breuer.*)

In examining more closely Fig 83 it is evident that the dark bands appear as single or double rows of dots or loops. The material of the bands is nucleoprotein containing desoxyribose nucleic acid. The gene, which is regarded by some as a giant nucleoprotein molecule, is presumably associated with a definite band. Studies of the chromosome changes mentioned above now make it possible to state confidently, in some cases, that a given gene lies within a region covered by a single band.

[1] C. Pavan and M E Breuer, Polytene Chromosomes in Different Tissues of *Rhynchosciara*, *J Heredity*, **43**:150–157, 1952.

Bridges originally counted a total of 2,650 bands in all four chromosomes of Drosophila This number agreed well enough at the time with the estimated number of genes in Drosophila, but subsequently Bridges made a more exhaustive study of the X chromosome, with improved technique, and found that there are many other faint bands which escaped detection before His revised map[1] of this chromosome shows 1,024 bands compared with 725 on his 1935 map.

More recently, map revisions have been made of the long chromosomes II and III by C B Bridges and Philip N. Bridges The latter author[2] has summarized the maps of all four chromosomes and finds a total band count of 5,072 He obtained this number by considering each double band as two There is some evidence, however, that each double band is a gene locus He therefore counted each double as one and obtained a total of 3,795 This is in general agreement with the present estimate of the number of genes in Drosophila

The origin of complex chromosomes containing thousands of genes arranged in a definite order presents an intriguing problem It seems necessary to suppose that during past ages, as life has progressed from the simple to the complex, new structures being added step by step, new genes must have been added also. Bridges offered the interesting suggestion that one type of chromosome change (*duplication*) may be the answer to the origin of new genes, since in certain sections of the salivary chromosomes he found blocks of bands duplicated in all their detail He argued that the genes in such duplicated blocks might subsequently mutate into genes having effects quite different from the original The net result would be the addition of new genes. So far, however, there is no evidence that this has actually happened, and the manner of origin of new genes must for the present remain speculative.

PROBLEMS

1. Is it possible to distinguish a gene mutation from a chromosome change by the type of phenotypic effect produced? Give an example or two.
2. Mention one type of chromosome change that may be inherited in the same manner as a gene mutation
3. How do you account for the fact that most new mutations, whether natural or induced, are injurious?
4. What is the presently held hypothesis as to the nature of the gene, both chemically and physiologically?
5. Give the various classes of evidence for the linear arrangement of the genes on the chromosomes

[1] C B. Bridges, A Revised Map of the Salivary Gland X-chromosome of *Drosophila melanogaster*, *J. Heredity*, 29:11–13, 1938

[2] P N. Bridges, A New Map of the Salivary Gland 2L-chromosome of *Drosophila melanogaster*, *J. Heredity*, 33:403–408, 1942.

6 What agents have been shown to increase the frequency of gene mutations? How do you account for the negative effects of other agents?

7. In what respects is mutation not an entirely random process, i e, to what extent is the type of mutation predictable?

8 Why is polyploidy in animals rare as compared to its frequency in plants?

9 List the animals mentioned in which polyploid species or races are found in nature.

10. Is it possible to produce to order a specific mutation by use of radiation or chemicals? Explain.

11. Give an estimate of the number of genes in Drosophila

12. Show by diagram four distinct types of chromosome changes

13

INBREEDING AND CROSSBREEDING

The term inbreeding usually refers to the mating of two closely related individuals, such as first cousins or nearer of kin, while crossbreeding is defined as the mating of unrelated individuals, each from a different variety or different species Strictly speaking, however, any two individuals are related if they have even one ancestor in common. Obviously, various degrees of inbreeding and crossbreeding exist The number of common ancestors and their recency furnish a measure of the degree of inbreeding

Two important questions arise in any discussion of inbreeding and crossbreeding First, why does the former automatically tend to make a population homogeneous or purebred—as it is known to do—while the latter tends to make a population less homogeneous? Second, how are we to explain the well-known fact that inbreeding tends to bring about a decline in vigor, while crossbreeding tends to increase the vigor of a race or species? Thanks to a knowledge of Mendel's laws we now have answers to both questions

Long before Mendel's time, animal and plant breeders came to the definite conclusion that close inbreeding usually was detrimental to the offspring and that a certain amount of crossbreeding was beneficial Nevertheless, the leading breeders of domesticated animals at times practiced close inbreeding because they found from experience that this was the easiest way of fixing a desired type

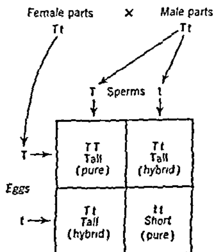
Likewise, the lawmakers in most human societies—if we correctly judge the motives behind the laws—came to the conclusion that inbreeding was detrimental to the race, for the laws and customs of most peoples have forbidden and still forbid the marriage of certain near relatives

From time to time, however, frequent exceptions had been noted to the rule that inbreeding was injurious and that crossbreeding was beneficial, but for these exceptions no logical explanation was at hand. By the application of Mendel's laws we are now able readily to harmonize such seeming conflicts.

EFFECTS OF SELF-FERTILIZATION

The closest possible type of inbreeding is self-fertilization, which occurs normally in many hermaphroditic plants, such as peas, wheat, barley, oats, and rice, and in a number of invertebrate animals With organisms having separate sexes, the closest type of inbreeding is backcrossing to a single homozygous parental type Beginning with these extreme cases there is a series of possible matings showing ever-decreasing degrees of relationship and ending finally with matings between distinct varieties and species. Thus the dividing line between inbreeding and crossbreeding is not a sharp one. For practical purposes, however, there is an important distinction, as will appear below

It may be recalled that Mendel, during the course of his experiments on peas, tested out 22 varieties of peas purchased from seedsmen and found every one of them true-breeding This result, in any plant other than a self-fertilizing one, would have been a practical impossibility, in a self-fertilizing plant, however, it is not especially remarkable Self-fertilization automatically tends to make a population pure-breeding It does this by the simple process of segregation of the genes according to Mendel's first law. For example, let us consider the simplest possible case, a plant that is hybrid with respect to only one gene (*Tt*) Let *T* stand for tall and *t* for short Both the egg-producing part and the sperm-producing part of the hybrid are (*Tt*) The process of reproduction in this plant may therefore be represented by the accompanying diagram.



In the first generation the hybrid parent has given rise to offspring of which 50 per cent are pure-breeding and 50 per cent hybrid. In the next

generation of self-fertilization we obtain the following result (assuming that each plant produces the same number of offspring):

TT	Tt	Tt	tt
↓	↓	↓	↓
4 TT	1 TT	1 TT	4 tt
	2 Tt	2 Tt	
	1 tt	1 tt	
Totals	6 TT	4 Tt	6 tt

Twelve individuals in this generation are pure-breeding and four are hybrids (75 per cent 25 per cent) Thus in the second generation the percentage of hybrids has been reduced again by one-half

In the third generation the percentage of hybrids will be still further reduced by one-half, resulting in 87.5 per cent purebred to 12.5 per cent hybrid This process will continue until by the tenth generation 99 9 per cent will be purebred, and only 0.1 per cent (one in a thousand) hybrid. As the process continues, it is obvious that the percentage of hybrids in the population will soon become infinitesimally small. For all practical purposes, the self-fertilizing organism will be 100 per cent purebred (homozygous) (Fig 84).

It could readily be shown, if space permitted, that the same rule holds good if two, or any other number of pairs of genes, are chosen for observation simultaneously In each generation of self-fertilization the percentage of homozygosis as a whole is halved. Theoretically, in the absence of selection there will always be a few heterozygotes left. But if selection accompanies the breeding—as it naturally does in breeding domesticated varieties—the plant can be made 100 per cent pure-breeding for any desired characteristic. Self-fertilization plus selection are no doubt the explanation of the purity of Mendel's varieties of peas.

This theoretical result agrees well with the practical results of self-fertilization in plants During the first few generations of inbreeding, in plants that normally cross-fertilize, there is a striking effect apparent in the reduction in vigor and the increase in homogeneity; but after about seven to ten generations, little further change is noted.

A great many plants, such as corn and clover, as well as all the higher animals, are normally cross-fertilizing. This is true even in most of those that are hermaphroditic The chief advantage of cross-fertilization over self-fertilization to the organisms themselves is the greater opportunity for the appearance of new and better combinations of genes. A necessary consequence of cross-fertilization, however—in the absence of close in-

breeding—is the accumulation of injurious recessive mutations, because rare recessive genes are usually concealed by normal dominant genes It is only when the recessive gene happens to be present in both parents that the offspring show it The general rule is, as we have noted, that recessive genes are injurious Consequently, when a normally cross-fertilizing species, for example corn, is self-fertilized, opportunity is at once

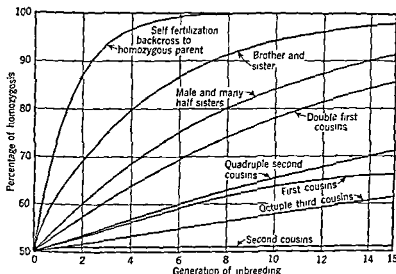


Figure 84. Curves showing increase in homozygosis as a result of inbreeding in successive generations under various systems of mating, starting with individuals that are 50 per cent homozygous The percentage reduction in heterozygosis per generation in the various types of mating are self-fertilization, 50 per cent, brother-sister, 25 per cent the first generation and 19 1 per cent thereafter, male and many half sisters, 11 0 per cent, double first cousins, 8 0 per cent, quadruple second cousins, 3 6 per cent, first cousins, approach toward fixation at a decreasing rate; octuple third cousins, 1 7 per cent, second cousins, to 98 per cent of the initial value after any number of generations (*From Wright, The Effects of Inbreeding and Crossbreeding on Guinea Pigs, U S Dept. Agr Bull* 1121, 1922.)

opened for these accumulated recessives to show their presence The result is more likely to be injurious than beneficial

On the contrary, in a self-fertilizing plant such as peas, there is a constant process of self-purification in every generation As new recessive mutations arise they are at once exposed in one-fourth of the offspring, and if the mutants are not fit, they perish. Only in the hybrids will the recessive persist, and as noted above, in a constantly decreasing percentage of individuals. For this reason, in an organism that is normally self-fertilizing, the process of self-fertilization causes no harm.

We may conclude, therefore, that inbreeding in itself is not detrimental. It is hazardous only to the extent that undesirable recessive genes are present in the original stock If the stock is free from these, inbreeding of the closest possible type may go on indefinitely without causing harm. The conflicting results from inbreeding in species that are self-fertilizing as compared with those that are cross-fertilizing are thus readily explainable An example from mammals will illustrate further the points here considered

BROTHER-SISTER MATINGS IN GUINEA PIGS

Among the most interesting and extensive investigations on the effects of inbreeding and crossbreeding in mammals is a series of experiments on guinea pigs, begun in 1906, by the U S Department of Agriculture[1] at Washington Thirty-five healthy and vigorous females were selected from general breeding stock and mated with a smaller number of similarly selected males The matings were numbered separately, and the offspring of each mating were kept separate and mated exclusively brother to sister This was continued generation after generation The 35 matings thus became the foundation of 35 "families." The only subsequent selection consisted in picking the two best for mating in case there were more than two in a litter Twelve of these foundation families were terminated for one reason or another before the experiment got well under way. Of the 23 remaining families, one became extinct after five years, one after eight years, three after nine years, and three after eleven years. At that time (1917), owing to lack of space, five of the remaining families were selected for perpetuation, the others were discarded.

The growth of a family, generation after generation, reminds one of the growth of a tree: each mating is a bud or twig; some of these twigs perish at once; others give rise to secondary twigs; some of the secondary twigs die for one reason or another; a few twigs grow into large branches with many sub-branches and twigs In any generation, however, only a few are destined to have living descendants a number of generations hence This is well shown in the partial pedigree of one of these inbred families (Fig 85). Note that the pedigree shows that all of the animals are descended from a single pair in the twenty-third generation of brother-sister mating

Two striking results followed the close inbreeding of guinea pigs First, each family gradually became more homogeneous While this process was

[1] Sewall Wright, The Effects of Inbreeding and Crossbreeding on Guinea Pigs, *U.S Dept. Agr. Bulls.* 1090 and 1121, 1922, Sewall Wright and O N. Eaton, The Persistence of Differentiation among Inbred Families of Guinea Pigs, *U S Dept Agr Tech. Bull.* 103, 1929.

going on there was a gradual elimination of sub-branches, as shown in Fig. 85. The increasing homogeneity within each family was accompanied by a notable differentiation among the families, as described below. Second, there was a decline in vigor during the first nine years, covering about 12 generations This decline applied to weight, fertility, and vitality of the young.

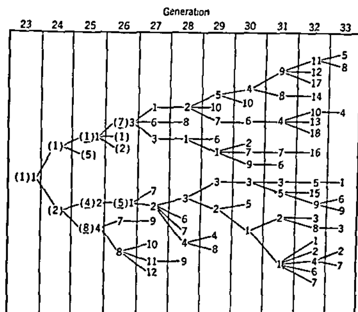


Figure 85. Pedigree of an inbred line of guinea pigs (Family 13) from the twenty-third to the thirty-third generation of straight brother-sister mating. The numbers on the family tree represent mating numbers in a given generation those in parentheses are Washington numbers, those underlined represent matings brought to the University of Chicago in 1926 by Wright Note the extinction of numerous lines.

During the second nine years of inbreeding there was no further decline in vigor of the inbred animals as a group This stability was taken to indicate that after 12 generations the families had become essentially purebred, i e , no longer heterozygous with respect to many genes (Fig 84). New mutations were apparently not frequent enough to have much effect

There was found no evidence of heredity of general vigor as a unit. The vigor of a family in one respect was largely independent of its vigor in other respects Thus Family 13 (Fig 86), which had the heaviest animals and the largest litters, was next to the poorest in resistance to tu-



Figure 86. Male of Family 13, belonging to the eighteenth generation of brother-sister mating The heaviest animals and the largest litters came in this family It was above the average in most other respects but was next to the poorest in resistance to tuberculosis The large amount of white is characteristic (*From Wright, The Effects of Inbreeding and Crossbreeding on Guinea Pigs, U S. Dept Agr. Bull* 1090, 1922.)



Figure 87. Male of Family 2, belonging to the twelfth generation of brother-sister mating. This family was characterized by frequent but rather small litters, heavy mortality at birth but great vitality and longevity thereafter. It was second in resistance to tuberculosis. (*From Wright, The Effects of Inbreeding and Crossbreeding on Guinea Pigs, U S Dept. Agr Bull.* 1090, 1922)

berculosis. The animals in Family 2 (Fig 87) were the lightest in weight; there were frequent but rather small litters, heavy mortality at birth, but great vitality and longevity thereafter. This family was second in resistance to tuberculosis

As a result of the inbreeding, each family came to be extremely homogeneous with respect to such characteristics as color of hair, eye color,

prominence of eyes, body conformation (one family was decidedly sway-backed, Fig. 88), and even temperament (Family 2 was noticeably more nervous and active than Family 13) Differentiation of the inbred families was by no means limited to external characters Strandskov[1] has made a study of internal organ differences in Family 2 and Family 13 The liver, lungs, and heart were significantly heavier in Family 13 than in Family 2, but this seemed to be correlated with the greater body weight of Family 13. The thyroids, adrenals, and spleen of the two families were

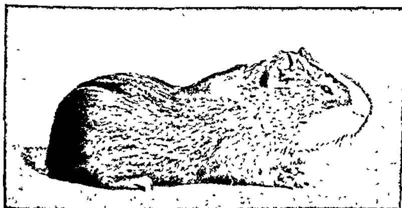


Figure 88. Male of Family 39, belonging to the thirteenth generation of brother-sister mating The small amount of white and the sway-back are characteristics fixed in this family Other characteristics are the greatest success in bearing young alive, but lack of success in rearing them, irregularity in producing litters, and the greatest susceptibility to tuberculosis. (*From Wright, The Effects of Inbreeding and Crossbreeding on Guinea Pigs, U S Dept. Agr Bull.* 1090, 1922)

found to differ not only in size but in shape (Fig 89) Strandskov makes the reasonable suggestion that these organs may be affected by genetic factors which are independent of those which determine general body size. He points out that if no other differences had been found between Family 2 and Family 13 the two families could readily have been distinguished by the differences in size and shape of the adrenals Those of Family 2, although the lighter of the two families, are significantly heavier than those of Family 13 The left adrenal of Family 2 is thick and triangular in cross section, as shown in Fig 89, whereas that of Family 13 is thin and flat That of Family 13 has a characteristic indentation on its mesial side. It is tempting to speculate upon the possibility of there being physiological differences in these and other glands, correlated with differences in growth and behavior of the two families

[1] H. H Strandskov, Inheritance of Internal Organ Differences in Guinea Pigs, *Genetics*, 24:722-727, 1939

In a further study Strandskov[1] made a comparison between 16 skeletal measurements of 20 males and 20 females of Family 2 and Family 13 He found significant differences in the families in 10 of the 16 measure-

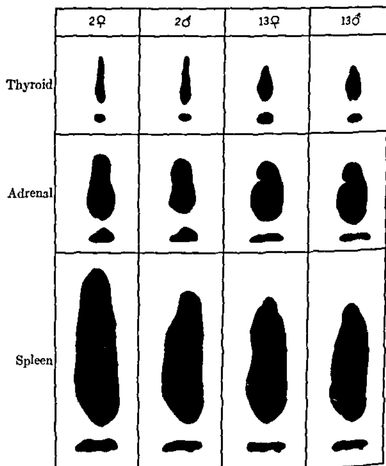


Figure 89. Drawings showing differences in the size and shape of thyroid, adrenal, and spleen of two highly inbred families of guinea pigs (Families 2 and 13) (*From Strandskov, Inheritance of Internal Organ Differences in Guinea Pigs, Genetics,* 24:722–727, 1939.)

ments. There was evidence that some of the differences were due to general growth factors and some to specific factors that act on local parts The humerus, the femur, the tibia, and some of the cranial bones seemed to be especially affected by local factors.

[1] H H. Strandskov, Skeletal Variations in Guinea Pigs and Their Inheritance, *J. Mammalogy,* 28:65–75, 1942

In all respects in which each inbred family came to be distinguished, the mechanism which brought about uniformity probably was the same, namely, the segregation, assortment, and recombination of genes and the gradual increase in homozygosis.

The theoretical rate at which continued brother-sister matings increase homozygosity has been calculated by a number of investigators. According to recent calculations made by Wright the reduction in the proportion of heterozygous gene pairs closely approximates 19.1 per cent per generation after the first generation, in which the reduction is 25 per cent (Fig. 84). Although this rate is much slower than the 50 per cent per generation found in self-fertilization, it is still so rapid that after 10 generations of brother-sister mating, starting with organisms that are 50 per cent homozygous, about 94 per cent of all gene pairs are homozygous. We see, therefore, why such inbreeding produces its greatest effect during the earlier generations, and relatively little effect if continued beyond 10 or 12 generations.

The results of the guinea pig inbreeding experiments are in good agreement with those from other mammals and from Drosophila. The decline in vigor, including the extinction of certain lines, follows largely from the segregation and fixing (making homozygous) of recessive genes, which are on the whole injurious to the species. But along with the fixing of such recessives there may also be a fixing of gene pairs which are indifferent or beneficial. It is a matter of chance as to what combination of gene pairs a family finally comes to possess, except that selection is always at work weeding out combinations that are not well adapted to the conditions of life.

There is a common belief that inbreeding causes the production of monstrosities and defectives. In the guinea pig experiments relatively few of these were produced, either by the inbred families or by the controls. It was found, however, that the tendency to produce a given type of monstrosity was characteristic of certain families, but such a tendency had no connection with the vigor of the family in other respects. The two feeblest families were almost free of abnormalities, while the most vigorous family (Family 13) produced 30 per cent of the cyclopean (one-eyed) monsters, 5 per cent of births in this family being monsters of this type. Another family produced most of the eyeless young, and still another had several young with rudimentary legs. There was evidence of hereditary tendencies within the families toward the production of these abnormalities. On the question of the relation of inbreeding to the origin of monstrosities Wright states, "There was no evidence that inbreeding has any specific causal connection with the origin of the monsters. Inbreeding seems merely to have brought to light genetic traits in the original stock."

HYBRID VIGOR (HETEROSIS)

The classic example of hybrid vigor is the mule. This animal is a species hybrid produced by crossing the horse (*Equus caballus*) with the ass (*Equus asinus*) The mule combines some of the superior qualities of both species it has much of the size, speed, strength, and spirit of the horse, along with the sure-footedness, lack of excitability, endurance, and ability to thrive on poor food which are characteristic of the ass This combination of traits gives to these hybrid animals a unique value for certain types of work For instance, at the Grand Canyon of the Colorado River in Arizona, herds of mules are maintained for carrying tourists over the trail from the rim to the river, one mile below Horses are not used for this work because of the danger of their becoming frightened by falling rocks or other disturbances and going over a precipice. Because of their superior quality as work animals mules bring a higher price than horses.

The mule is rather an exceptional case, however, since there are very few species hybrids of economic importance among domesticated mammals. Like most species hybrids in mammals, the mule is sterile because normal reproductive cells fail to develop. There seem to be no recorded *cases of fertile male mules; female mules have occasionally* produced colts, either by the stallion or the jack. In some other species hybrids, e g , the catalo, from the cross between bison and cattle, the female is fertile and *the male is sterile* Among mammals, *it is usually impossible* to obtain a hybrid by crossing one genus with another. Such wide crosses as the cat (*Felis domestica*) with the dog (*Canis familiaris*) or the jackrabbit (*Lepus californicus*) have never been obtained

As mentioned in Chap. 1, the term hybrid is properly applied also to the offspring of two subspecies or two varieties of the same species Such varieties may differ in only one gene or, as is commonly the case, they may differ in a number of genes. Let us now consider hybrid vigor as it is expressed in crosses between varieties

Hybrid Vigor in Guinea Pigs

As a result of breeding experiments with plants and animals, it is now generally accepted that hybrid vigor, in certain cases at least, has a simple explanation in the operation of Mendel's laws. The experiments with guinea pigs, described in the previous section, included an investigation of hybrid vigor The results are very clear-cut in their demonstration of the increase in vigor following the crossing of two pure breeds. Crosses were made among five of the inbred lines or breeds of guinea pigs produced by brother-sister matings It will be recalled that in these experiments continuous mating of brothers with sisters was accompanied by a decline in all of the elements of vigor that were studied. These elements

of vigor included the percentage born alive, the percentage raised to weaning, the birth weight, the rate of gain in weight, adult weight, size of litter, and number of litters per year The inbred animals as a group came to be distinctly inferior to the random-bred control stock, a stock in which matings closer than second cousins were not made (Fig 84), in all these respects, as well as in resistance to tuberculosis Two of the five

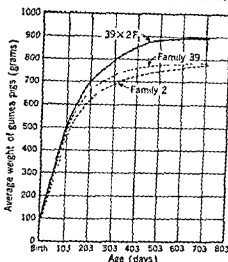


Figure 90. Growth curves of inbred guinea pigs of Families 2 and 39 and the F_1 hybrids from Family 39 males × Family 2 females, illustrating hybrid vigor (*From Eaton, Effect of Crossing Inbred Lines of Guinea Pigs, U.S Dept Agr Tech Bull* 765, 1941)

inbred families, however, were more resistant to tuberculosis than the controls.

It was found also that the various elements of vigor and weakness were inherited independently of each other, and that these had become fixed in almost all of the possible combinations in the various families; though there was no evidence of hereditary differences in general vigor

In addition, a conspicuous differentiation was evident among the families in such characteristics as color, number of toes, and tendency toward the production of particular types of monsters Each family came to be characterized by a particular combination of traits, usually involving strength in some respects and weakness in others These results were interpreted in accordance with Mendel's laws of heredity.

Crosses between different inbred families showed marked improvement in the offspring over both parental inbred families, in every respect In

the case of adult weight and resistance to tuberculosis the improvement appeared to its full extent in the offspring of the first cross. The hybrid young were at least as resistant to tuberculosis as the more resistant parental family. In some cases the young were more resistant than either parental family Resistance was dominant over susceptibility.[1]

The improvement in the various elements of vigor affecting the number of young raised to weaning per year added up to produce an increase

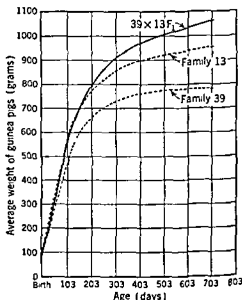


Figure 91. Growth curves of inbred guinea pigs of Families 13 and 39 and the F_1 hybrids from Family 39 males × Family 13 females, illustrating hybrid vigor. (*From Eaton, Effect of Crossing Inbred Lines of Guinea Pigs, U.S. Dept. Agr. Tech. Bull.* 765, 1941)

of over 80 per cent in the number of young raised, so that the hybrids from inbred family crosses were considerably superior to the random-bred controls in this respect. Experiments confirming and extending these studies with respect to growth and several other traits have been published by Eaton[2] (Figs. 90 and 91)

Wright concluded from his analysis of the various crosses that the results just described were all the direct or indirect consequence of the

[1] Sewall Wright and Paul A. Lewis, Factors in the Resistance of Guinea Pigs to Tuberculosis, with Especial Regard to Inbreeding and Heredity, *Am Naturalist*, 55:20–50, 1921

[2] O. N. Eaton, Effect of Crossing Inbred Lines of Guinea Pigs, *U.S Dept. Agr. Tech. Bull.* 765, 1941.

Mendelian mechanism of heredity, that the fundamental effect of inbreeding is the automatic increase of homozygosis, and that an average decline in vigor is the consequence of the observed fact that recessive genes are more likely to be injurious than are their dominant alternatives He concluded further that the differentiation among the families

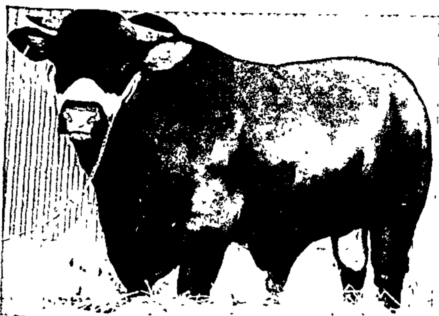


Figure 92. Two-year-old Santa Gertrudis bull, member of a new breed of beef cattle produced on the King Ranch in Texas by crossing Indian Brahman cattle with shorthorns and selecting for certain traits Among the recognized characters of the breed are red coat; loose, thin hide with surface area increased by neck folds and sheath; broad prominent brisket, resistance to heat and parasites of hot climates. (*Courtesy of King Ranch, Texas.*)

is due to the chance fixation of different combinations of the genes present in the original random-bred stock and that crossing of inbred families causes an improvement because each family supplies some dominant genes lacking in the other

Wright suggested that the method of close inbreeding, followed by crossbreeding, would have important applications in the improvement of livestock The method had in fact been used by the pioneer breeders more than a century earlier on a less intensive scale in the founding of many of the pure breeds of livestock. Its use is growing in the production of poultry, hogs, dairy cattle, and beef cattle (Fig 92). The most remarkable results of the method thus far, however, have come from its appli-

cation to crop plants such as corn and sugar cane, in which phenomenal increases in yields have been obtained from hybrids.

Hybrid Corn

Our most striking example of the application of classical genetics to an economic problem is the production of hybrid corn. An American geneticist, George H. Shull,[1] is given credit for first advocating (1909) the use of self-fertilized lines in the production of commercial seed corn. As a botanist with the Carnegie Institution at Cold Spring Harbor, New York, he was interested in the inheritance of quantitative characters and chose to experiment with corn. Varieties of this plant differ greatly in many characters, including the number of rows of seeds on the cob. By self-pollination Shull established true-breeding (homozygous) lines for this character as well as for other characters. Each of these inbred lines not only became very uniform but also suffered a reduction in various elements of vigor, such as size of plant, yield of seed, etc.

Upon crossing one of his inbred lines with another, Shull found that the resulting F_1 hybrids showed great increase in vigor. Moreover, the F_1's of the same cross were remarkably uniform. Incidentally, this uniformity has a great practical advantage in the production of sweet corn for the market and for canning: since all of the ears mature at about the same time, the problem of harvesting is simple. For the home gardener who wants a continuous supply of green corn a series of hybrids that mature at regular intervals over a period of one month has been developed.[2]

Shull attributed the hybrid vigor to the stimulating effect of heterozygosity per se. How much of the hybrid vigor may be due to the superiority of the heterozygote of a pair of alleles over either homozygote is a difficult question. Examples of such an effect (known as overdominance) have been reported in a number of different organisms. The explanation of hybrid vigor most often given today, however, is that vigor depends upon many dominant genes and that each inbred line brings into the hybrid certain dominant favorable genes lacking in the other. The two theories are not mutually exclusive.

In some of his experiments Shull had produced "double crosses" by mating two of his F_1 hybrids. In 1917 D. F. Jones[3] pointed out the practical possibilities of the double-cross, or four-way, hybrid method in the production of commercial seed. The method proved to be economically

[1] G. H. Shull, Beginnings of the Heterosis Concept, in John W. Gowen (ed.), "Heterosis: A Record of Researches Directed toward Explaining and Utilizing the Vigor of Hybrids," Iowa State College Press, Ames, Iowa, 1952.

[2] R. W. Singleton, Hybrid Sweet Corn, *Connecticut Agr. Expt. Sta. Bull.* 518, 1948.

[3] Edward M. East and Donald F. Jones, "Inbreeding and Outbreeding: Their Genetic and Sociological Significance," J. B. Lippincott Company, Philadelphia, 1919.

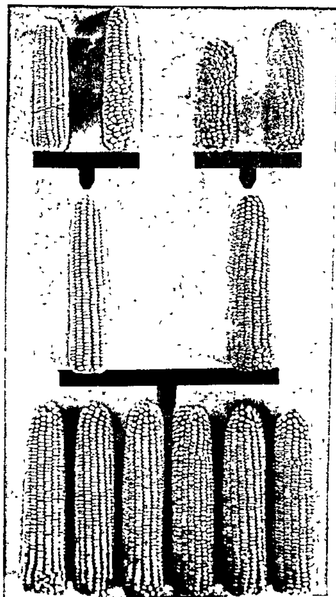


Figure 93. The double-cross method of producing hybrid seed corn Four inbred lines contribute equally to produce the commercial seed (*Courtesy of Donald F. Jones, Connecticut Agricultural Experiment Station.*)

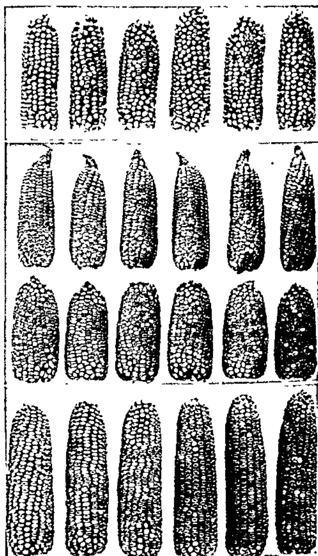


Figure 94. Representative ears of four inbred lines of maize after 11 generations of self-fertilization, showing distinctive differences among the four lines but uniformity of type within each line. (*Courtesy of Donald F. Jones, Connecticut Agricultural Experiment Station*)

profitable. Today most of the seed planted in the United States in the production of ordinary field corn, as contrasted with sweet corn, is obtained by the double-cross method (Fig 93).

Numerous inbred lines of corn are produced by self-fertilization In these inbred lines there is a rapid decline in vigor, because corn is natu-

rally cross-pollinated and therefore carries a load of accumulated deleterious recessive genes; but out of many inbred lines a few give fair yields (Fig 94). Four superior inbred lines are chosen, lines A, B, C, and D Line A is crossed with line B; and line C is crossed with line D The two resulting hybrids are then crossed, the seed from the second cross becomes the commercial seed (Fig. 95) The seeds of the first cross are not used for crop production with ordinary field corn because they are often

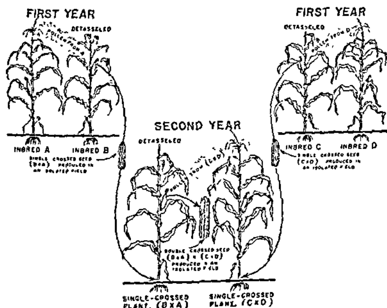


Figure 95 Method of producing double-cross commercial hybrid seed corn. (*From Sprague, Production of Hybrid Corn, Iowa State Coll Agr Expt. Sta Bull P48*, 1942)

small and poorly developed and their numbers may be low, owing to the inbreeding of the parents. The crossing of the two F_1 hybrids, however, produces a large amount of seed The second-generation hybrids produced from this seed are, of course, variable because their parents are hybrids; any disadvantages resulting from their variability, however, are more than offset by the abundant yield (Fig 96).

Corn produced from hybrid seed is not planted the following year. Experience shows that if this is done there is a marked decline in vigor and increase in variability.

The development of the inbred strains and the production of hybrid seed from them is naturally an expensive process Nevertheless, the results more than justify the labor, since hybrid corn frequently yields 25 to 30 per cent more per acre than ordinary open-pollinated corn The use

of hybrid seed has steadily increased in this country since the early 1930s (Fig 96). By 1949 about 77.6 per cent of the acreage was in hybrid corn At the present time nearly 100 0 per cent of all corn grown in the United States is from hybrid seed

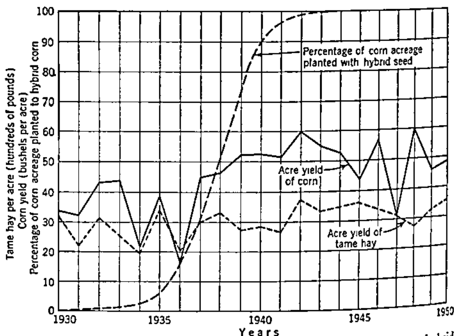


Figure 96. Curves showing increased yield of maize per acre in Iowa after hybrid seed came into general use in the 1930s, compared to a near-constant yield of tame hay, in which no similar breeding method has been practiced. *(From Sprague, in John W. Gowen (ed.), "Heterosis," Iowa State College Press)*

MARRIAGE LAWS PREVENT CLOSE INBREEDING IN MAN

In the United States, legislation on marriage is a function of the several states. All of the states prohibit marriages between blood relatives closer than first cousins; a majority prohibit marriages of first cousins Those states that permit cousin marriages are all in the South and East except California in the Far West. The newer states in the Middle West and Northwest without exception prohibit cousin marriages. A few states extend the prohibition to first cousins once removed (i e., a marriage between an individual and a child of his first cousin), and one, Oklahoma, prohibits the marriage of second cousins (the children of first cousins) [1]

Nearly half the states prohibit a man's marrying certain classes of rel-

[1] I am indebted to Mrs. A. C Buchanan, Director of Research Service, Encyclopaedia Britannica, for furnishing a compilation of the laws and statutes concerning consanguineous marriages in the United States and foreign countries

atives-in-law such as his wife's daughter, his wife's mother, or his stepmother. The same prohibitions apply to women within corresponding degrees Strange as it may seem, in general these are the same states that permit cousin marriages. Whatever the reasons for prohibiting the marriage of relatives-in-law, such reasons, of course, have nothing to do with the hereditary qualities of expected offspring The model for such statutes is no doubt the Mosaic law as contained in the eighteenth chapter of Leviticus The Mosaic law makes no provision against cousin marriages, but prohibits marriages between various classes of relatives-in-law, as well as blood relatives nearer than first cousins

In most European countries the marriage laws appear to be patterned after the Mosaic law. All, save a few of the smaller countries in the south of Europe, permit cousin marriages, as do also the British Dominions, Japan, and countries which follow Mohammedan law China, on the other hand, prohibits the marriage of cousins China forbids marriages between persons having the same surname, as did some of the tribes of North American Indians and the Aborigines of Australia

Ideas condemning the marriage of near of kin must have had a very ancient origin, since the customs of most primitive tribes enforce certain restrictions There is no unanimity on the question of cousin marriages, for among some primitive peoples cousin marriages are prohibited, while among others they are highly favored Curious exceptions regarding marriages of the nearest of kin are found among a few primitive tribes According to Bronislaw Malinowski,[1] marriages between mother and son or daughter and father are reported from certain tribes in Malaysia, in the Islands of the South Pacific, and in Africa Even better attested, according to this anthropologist, are the marriages between brother and sister in the Marshall Islands and Hawaii and, in ancient times, in the royal families of Egypt, Ireland, and the Inca Empire of South America

COUSIN MARRIAGES AND DEFECTIVES IN MAN

There is a widespread popular belief that the marriage of first cousins is likely to result in defective offspring On what evidence is this based? The question can best be answered from the examination of a concrete case

Amaurotic idiocy (see Chap 16) is a recessive defect in man. Torsten Sjögren[2] has made an exhaustive study of the juvenile form of this disease in Sweden, where he visited all the schools for blind children in search of cases. The fact that in Sweden family records have been kept

[1] "Encyclopaedia Britannica," article on Marriage

[2] Torsten Sjögren, Die juvenile amaurotische Idiotie Klinische und erblichkeitsmedizinische Untersuchungen, *Hereditas*, 14:197–425, 1930–1931.

in the churches for generations enabled him to prepare more than fifty pedigrees

Approximately one case of juvenile amaurotic idiocy was found for every 30,000 children In the population of Sweden as a whole only about 1 per cent of marriages were between first cousins, yet this 1 per cent was responsible for about 15 per cent of all the amaurotic children in Sweden Marriages between relatives other than cousins produced another 10 per cent of the amaurotics

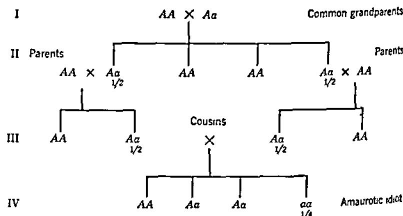


Figure 97 A typical pedigree covering four generations showing the path of a recessive gene from a single grandparent of two cousins to its expression in a child of the cousins. The probability of the appearance of the recessive trait in an individual of generation IV is found by multiplying together the five fractions ($\frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{4} = \frac{1}{64}$)

Clearly, the marriage of cousins has something to do with the occurrence of this rare recessive defect The relationship seems to be as follows All cases of amaurotic idiocy come from normal parents who are heterozygous for the gene, since defectives invariably die young and never reproduce. Cousins have two grandparents in common and therefore draw one-half of their genes from the same pool. With respect to any gene present in a single grandparent of two cousins, there is a chance of one in 16 that both cousins will inherit it from this grandparent. The demonstration of this relationship is shown in the accompanying example of a typical pedigree (Fig 97) Let a stand for the gene for amaurotic idiocy and A for the normal alternative gene. One grandparent is shown as a carrier of the defective gene; all the other grandparents are assumed to be free from it.

Let us now apply the law of probability under which the chance of occurrence of a series of events is equal to the product of the chances of

the individual events (Chap 2) We see that the chance of a person in generation II being a carrier (*Aa*) is one in two The chance of a person in generation III being a carrier (provided a parent in II is a carrier) is also one in two Hence the chance of a grandchild such as one of the cousins being a carrier is $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$. The chance of both cousins simultaneously being carriers is $\frac{1}{4} \times \frac{1}{4} = \frac{1}{16}$

With two cousins who are both carriers the chance is one in four of producing at each birth a child who is recessive (*aa*) Multiplying this probability by the probability that both cousins shall be carriers we get $\frac{1}{4} \times \frac{1}{16} = \frac{1}{64}$. This represents the chance of a child's showing any recessive trait, the gene for which was present in the heterozygous state in one, and only one, of the common grandparents of the two cousins and not present in any of the other grandparents.

In Sweden, approximately one child in 40,000 from unrelated parents is amaurotic. The frequency of carriers of gene *a* must, therefore, be about one in 100, because the chance of two such carriers marrying is only $\frac{1}{100} \times \frac{1}{100}$, or 1/10,000, and if such a marriage occurs the chance is one in four that the first child born will be amaurotic

The chance that one or the other of the two common grandparents of cousins will carry the recessive gene *a* is $\frac{1}{100} + \frac{1}{100} = \frac{1}{50}$ (one in 50) The chance that a cousin marriage chosen at random will produce an amaurotic child as the result of genes derived from a common grandparent is therefore $\frac{1}{50} \times \frac{1}{64} = 1/3{,}200$ There is also a very slight chance that both cousins will receive the gene for amaurotic idiocy from their other grandparents not held in common or from one of the two possible combinations of common grandparents with noncommon grandparents Without presenting the calculations of this slight chance we may say that by combining all of the chances mentioned above we obtain one chance in 3,061 as the probability of the birth of an amaurotic child from a cousin marriage chosen at random in Sweden This chance is approximately 13 times the chance of birth of such an individual from unrelated parents

Although the risk of this particular recessive showing up is rather small, even in cousin marriages, it must be remembered that there are hundreds of other rare recessive defects in man, and the gene for one or more of these will probably be present in a common grandparent. The rarer a recessive gene is in the population the greater is the effect of a cousin marriage in increasing the frequency of the trait as compared with its frequency from unrelated parents With relatively common recessive traits there is little risk of increasing the frequency with cousin marriages.

Among other rare recessive defects known to have a much higher frequency in children from cousin marriages than in children from unrelated parents are the following: albinism, xeroderma pigmentosum, total color blindness, Friedreich's disease, phenylketonuria, microcephaly, and

congenital ichthyosis Obviously, the popular prejudice against cousin marriages is based upon sound facts so far as the increased risk of defective offspring is concerned.

The picture of cousin marriages which we have just drawn has another side If inbreeding as exemplified by cousin marriages tends to bring into expression injurious genes which are already present in the stock, it likewise tends to bring into expression beneficial genes, since the mechanism of heredity is the same in both cases. One famous example of superior traits passing on to the children of cousins is found in the family of Charles Darwin. Darwin, who came from a distinguished English family, married his first cousin, also from a distinguished family. Of five sons who survived him, four became distinguished far above the average, and in ways that clearly indicate superior hereditary intellectual capacities

This family may also illustrate the outcropping of recessive defects, since according to one of Darwin's daughters,[1] in the family of ten children many were delicate and difficult to rear, and three died. She states that the last child, a son, was born without his full share of intelligence and died at about a year and a half of age, never having learned to walk or talk

All things considered, it seems that we are not justified in laying down a hard and fast rule against cousin marriages. In special cases the opportunity of preserving or concentrating superior qualities in the offspring may warrant taking some of the risks that naturally accompany such marriages

PROBLEMS

1. Why does inbreeding in species that are normally crossbred usually lead to a decline in vigor?
2. How is it possible for species that normally are self-fertilized to continue indefinitely with no decline in vigor?
3. Why does crossbreeding two distinct varieties or species usually result in a hybrid more vigorous than either parent?
4. What is usually the nature as to vigor and variability of the offspring produced by F_1 hybrids?
5. In his experiments with garden peas Darwin found that a cross between two individuals of the same variety resulted in no increase in height or fertility of the offspring Give an explanation of this result in terms of the gene theory
6 Darwin found that a cross between two varieties of peas resulted in a marked superiority in the vigor of the offspring over the self-fertilized plants of the same varieties Explain this by the use of the gene theory. Diagram the generations, using gene symbols of your own choosing
7. Explain by diagram, using two pairs of genes, how inbreeding in mammals, accompanied by rigorous selection, may result in no appreciable decline in vigor.
8. Show by diagram, using two pairs of genes, why the hybrid offspring of two

[1] "Emma Darwin, A Century of Family Letters, 1792–1896," edited by her daughter Henrietta Litchfield, Appleton-Century, 1915.

purebred varieties or of two species is usually no more variable than the parent varieties or species themselves

9. In some of the crosses between inbred families of guinea pigs the hybrids were larger than either inbred line and larger than the ordinary random-bred stock Explain this result by means of a diagram of matings and two pairs of hypothetical genes

10. Show by diagram, choosing two hypothetical characters and genes, in which two homozygous races differ, how to obtain, by crossing and selection, a race of organisms that is homozygous for a *combination of traits* superior to that of either parental type

11. Represent by means of the usual histograms or bar graphs the range of variability in some quantitative character such as skin pigmentation in man in the offspring of hybrids Show separately the range, assuming (*a*) that the difference between the original types depends upon a single gene pair, (*b*) that the difference depends upon two pairs of genes, and (*c*) that it depends upon three pairs of genes

12. If among the offspring of F_1 hybrids the two original pure types are seldom obtained, what can be said regarding the probable number of gene differences between the original types?

13. What method of breeding is necessary in order to produce a pure breed of mammals? Explain

14. Mention some important problem in biology which might be solved by the use of a completely homozygous stock of animals

15. Under what conditions would you advise against the marriage of first cousins?

16. What is the advantage of the double-cross method of producing hybrid seed corn compared to the single-cross method?

17. Why is the single-cross method preferred with sweet corn?

18. What is meant by *overdominance?* Give an example.

19. Assume that a man is heterozygous for an autosomal recessive gene Diagram and show your calculation of the chance that he and his first cousin have both inherited the same gene from one of their two common grandparents who was heterozygous for the gene

14

HEREDITY AND EVOLUTION

As used in biology the term *evolution* denotes the process of origination of the various kinds of plants and animals by descent from other kinds through the interaction of natural forces In contrast to the theory of evolution there is the theory of the separate creation of each species.

The earlier writers on evolution sharply separated the question of evolution from the problem of the origin of life. As to the origin of life, Darwin himself, who did more to establish the truth of evolution than any other man, publicly took a thoroughly orthodox view, as expressed in the closing sentence of his book "The Origin of Species":

> There is grandeur in this view of life, with its several powers, having been originally breathed by the Creator into a few forms or into one; and that, while this planet has gone circling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being evolved

But in a letter to his closest scientific friend, the famous English botanist Sir J D Hooker, in 1863 he writes,

> I have long regretted that I truckled to public opinion, and used the Pentateuchal term of creation, by which I really meant "appeared" by some wholly unknown process It is mere rubbish, thinking at present of the origin of life, one might as well think of the origin of matter.

Although the problems of the origin of life and the evolution of life are perhaps logically distinct, it seems probable, on the basis of recent researches on the filterable viruses, that the two problems will eventually merge into one In Chap 12 we considered the interesting resemblances between the viruses and genes and found that in some respects viruses appear to be intermediate between the living and the nonliving. Further intensive study of the gene may well result in important contributions to the problem of the origin of life.

MENDEL AND EVOLUTION

In Darwin's day very few people, biologists included, had come to accept evolution as a fact Darwin therefore felt it necessary to devote much of his energy to the marshaling of evidence in support of the fact



Figure 98. Charles Darwin in 1854 *(From Darwin and Seward, "More Letters of Charles Darwin," D Appleton & Company,* 1903)

of evolution The case he made out was so convincing that most biologists—as well as many of the laity—were converted to the idea of evolution as a fact. Mendel, as mentioned earlier, was a close student of Darwin's writings and undoubtedly accepted the existence of evolution, for in the introduction to his paper on peas he writes:

> It requires indeed some courage to undertake a labour of such far-reaching extent; this appears, however, to be the only right way by which we can finally reach the solution of a question the importance of which cannot be overestimated in connection with the history of the evolution of organic forms.

Near the end of Mendel's paper is the following statement:

The opinion has often been expressed that the stability of the species is greatly disturbed or entirely upset by cultivation, and consequently there is an inclination to regard the development of cultivated forms as a matter of chance devoid of rules, the coloring of ornamental plants is indeed usually cited as an example of great instability It is, however, not clear why the simple transference into garden soil should result in such a thorough and persistent revolution in the plant organism. No one will seriously maintain that in the open country the development of plants is ruled by other laws than in the garden bed. Here, as there, changes of type must take place if the conditions of life be altered, and the species possesses the capacity of fitting itself to its new environment

And finally, in his concluding remarks, while discussing hybrids in certain plant groups which are known to breed true in the same way that pure species breed true, he writes. "For the history of the evolution of plants this circumstance is of special importance, since constant hybrids acquire the status of new species"

Although the quoted statements indicate that Mendel accepted evolution as a fact, he was, according to his biographer Iltis, critical of some *of the theories proposed to explain the process of evolution* In particular he was skeptical of the theory of the inheritance of acquired characters, developed by Lamarck and adopted in part by Darwin. This skepticism, which was based upon Mendel's own experiments, has been fully justified by subsequent developments Although Darwin never knew of Mendel's work, the application of Mendel's laws has had a profound influence in recent years in confirming and extending the theory of natural selection, proposed independently by Darwin and his British contemporary A. R. Wallace in 1858.

NATURAL SELECTION

Since natural selection constitutes the core of our modern theories of evolution let us quote a summary of it by one of the originators of the theory as found in the introduction to "The Origin of Species" by Darwin.

As many more individuals of each species are born than can possibly survive; and as, consequently, there is a frequently recurring struggle for existence, it follows that any being, if it vary however slightly in any manner profitable to *itself*, under the complex and *sometimes varying* conditions of life, will have a better chance of surviving, and thus be *naturally selected*. From the strong principle of inheritance, any selected variety will tend to propagate its new and modified form . . . I am convinced that natural selection has been the most important, but not the exclusive, means of modification.

The statement is sometimes made today that biologists have abandoned the theory of natural selection Nothing could be farther from the truth Those in the forefront of research in heredity and its application to evolution are the stanchest supporters of natural selection—as witness the following statement from Professor Sewall Wright,[1] of the University of Wisconsin:

> The conclusion seems warranted that the enormous recent additions to knowledge of heredity have merely strengthened the general conception of the evolutionary process reached by Darwin in his exhaustive analysis of the data available 70 years ago [2]

Other leading investigators might be quoted to the same general effect. It is fair to state that natural selection is more firmly established now than ever before as one of the factors of evolution, although there is considerable difference of opinion as to its relative importance as compared with other factors

Let us now consider in more detail the theory of natural selection and its relationship to the principles of Mendelian heredity Referring back to Darwin's summary, we note that he there states several biological laws, which upon examination prove to be almost self-evident These laws are (1) the geometrical ratio of increase of all organisms, (2) the struggle for existence, (3) hereditary variations, and (4) the survival of the fittest

1. The Geometrical Ratio of Increase. By this is meant that tendency of every organism to reproduce itself at such a rate that its numbers in consecutive generations form a geometric progression Growth is thus by multiplication rather than by mere addition of a fixed number in each generation For example, if the population doubles in each generation, as it does under favorable conditions in man, the numbers in successive generations are as 1 2 4 8, etc., rather than in an arithmetical series such as 1 2 3 4 Some striking examples of this tendency may be cited

Among the many-celled plants a group of higher fungi known as puffballs have perhaps the highest rate of reproduction Some puffballs are said to reach several feet in diameter They are filled with tiny reproductive cells known as spores, which in a single individual, according to estimates, may reach the stupendous total of one million million (1,000,000,000,000) If each of these spores were to develop into a puffball only 1 inch in diameter, they would cover a combined area of 250 square miles, growing side by side in physical contact If in turn each of these individuals produced only 500 million spores, all of which developed into 1-inch

[1] Sewall Wright, Evolution in Mendelian Populations, *Genetics*, 16 97–159, 1931

[2] Theodosius Dobzhansky, "Genetics and the Origin of Species," 3d ed , Columbia University Press, New York, 1951

puffballs, they would cover in close contact a surface of 125 billion square miles, or more than 2,700 times the total land area of the earth

Again, in the wood-eating insects known as termites, the queen grows to an enormous size and becomes a veritable egg-laying machine. She is then incapable of locomotion and is zealously tended by the workers in the colony. Professor Alfred E Emerson, of the University of Chicago, an authority on termites, who has in preserving fluid the largest termite queen ever reported, has kindly supplied the following facts The queen referred to (a member of the species *Macrotermes natalensis*) was collected by Lang in the Belgian Congo in 1913. Her dimensions are length 101 mm., width 31 mm When taken from the termite hill, according to Lang, she laid about one egg a second. Termite queens live and lay eggs for a number of years. Egg laying is not continuous; nevertheless, entomologists have estimated that a single queen may produce more than one million offspring in her lifetime.

Man has a relatively slow rate of reproduction, yet during the past century or two we have seen his potentialities in this respect amply demonstrated For example, the population of Japan has grown as follows (using round numbers):

Population of Japan	
1846	27,000,000
1872	33,000,000
1893	41,000,000
1913	53,000,000
1923	60,000,000
1930	64,000,000
1939	73,000,000
1950	83,000,000

Since the Second World War there has been a growing concern on the part of the government of Japan with the problem of overpopulation. Under a 1948 law, marriage-consultation offices have been established, with physicians available to give advice on human heredity and on voluntary control of the size of the family. Reports indicate increasing practice of such limitation [1] The birth rate has fallen from a postwar high of 34.3 per 1,000 in 1947 to 21.4 per 1,000 in 1953.

The history of population increase in the United States is even more remarkable, although it is complicated by a considerable amount of immigration. Official United States Census figures (to the nearest 100,000) are as follows:

[1] Yoshio Koya, Minoru Muramatsu, Sakito Agata, and Maruo Suzuki, A Survey of Health and Demographic Aspects of Reported Female Sterilization in Four Health Centers of Shizuoka Prefecture, Japan, *Milbank Mem Fund Quart.*, 33:368–392, 1955

POPULATION OF CONTINENTAL UNITED STATES

1790	4,000,000
1800	5,300,000
1820	9,600,000
1840	17,100,000
1860	31,400,000
1880	50,200,000
1900	76,000,000
1910	92,000,000
1920	105,700,000
1930	122,800,000
1940	131,700,000
1950	151,100,000
1954	163,900,000*

*Estimate

It is obvious from the above statistics that the population of the United States actually more than doubled in each generation (25 years) during the first 75 years of our history Malthus, British author of the famous book "An Essay on the Principle of Population," first published in 1798, wrote a summary of his views in 1830,[1] in which he points out that "The best proof that can be obtained of the capacity of mankind to increase at a certain rate, is their having really increased at that rate" He analyzes at length the first four censuses of the United States and presents the documentary evidence that immigration was small (about 10,000 per year) and that aside from immigration the population increased at the rate of 100 per cent per 25 years He chose the United States as the best example of unusually favorable conditions for rapid growth in population because

> In the United States, not only is there an abundance of good land, but from the manner in which it has been distributed, and the market which has been opened for its produce, there has been a greater and more constant demand for labor, and a larger portion of necessaries has been awarded to the laborer than in any of those other countries which possess an equal or greater abundance of land and fertility of soil

After 1880 the rate of increase in the population of the United States fell rapidly, though irregularly, from 30 1 per cent for the decade 1870–1880 to 7.2 per cent for the decade 1930–1940 The great economic depression of the 1930s probably played a part in this decline, mainly through its adverse effect on the birth rate (Fig 99). Also during this decade 46,518 more persons left the United States than entered The

[1] Thomas R Malthus, "A Summary View of the Principle of Population," 1830, reprinted in D V Glass (ed), "Introduction to Malthus," C. A. Watts & Company, Ltd , London, 1953

fluctuations in the birth rate in the United States are largely due to voluntary limitation of size of families. The birth rate rose rapidly with the opening of the Second World War, declined rapidly during the last few years of the war, and again rose still more rapidly after the close of the war, reaching a maximum in 1947 Since 1948 it has remained fairly steady at about 25 births per 1,000 population This rather high rate for a modern industrial nation will probably not last, judging by the decline

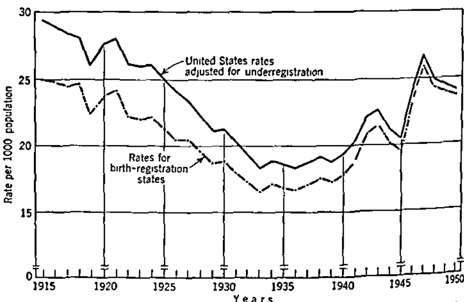


Figure 99. Birth rates for the United States from 1915 to 1950 In 1950 birth registration estimated 97 8 per cent complete (*U S. Department of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics*)

in the marriage rate since 1947. Although there is no certainty in predicting the future by the past, it is probably safe to say that there will be no doubling of the population of the United States in the next fifty years as there has been in the past fifty The curve shown in Fig 100 was drawn by Pearl and Reed in 1920, following the preceding census figures, and was projected forward to the year 2100 in accordance with the past pattern of growth So far, the census counts after 1920 have followed the curve fairly closely.

2. The Struggle for Existence. This expression was used by Darwin in a metaphorical sense to describe the complex relationships of organisms one to another, as well as to their physical environment. For example, a desert plant must struggle to conserve water, and man must struggle to obtain food and shelter and to resist the attacks of parasitic diseases The struggle may be among members of a given species as well as among

distinct species Even though it were possible to have complete cooperation within a species there would always be potential enemies and dangers from without against which a struggle would be necessary.

3. Hereditary Variations. Our study of heredity has shown us that each individual is unique (identical twins, triplets, etc excepted) and that much of this uniqueness is due to a difference in the gene make-up

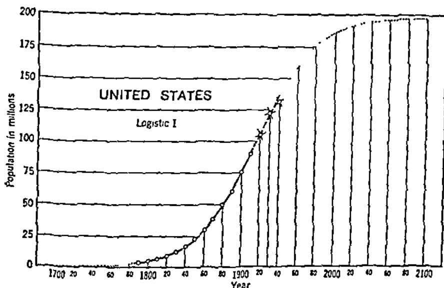


Figure 100. The census counts of the population of the United States from 1790 to 1940 (*circles*). The smooth curve is the logistic of an equation fitted to the census counts from 1790 to 1910. The broken lines show the extrapolation of the curve beyond the data to which it was fitted The 1950 census figures fall very close to the predicted value. (*From Pearl, Reed, and Kish, Science,* 92.487, 1940)

of the individual. Although Mendel's laws of heredity and the gene concept were unknown to Darwin, he recognized that there were two types of variations—those due to environmental differences (which he called environmental modifications) and those due to hereditary differences (hereditary modifications) Darwin's greatest error as we view it today was in considering that certain changes induced by the environment or by exercise were converted into hereditary changes (the inheritance of acquired characters) But as already pointed out, the existence of such hereditary variations is the important fact, and for the purposes of natural selection it makes no difference how the variations are produced.

4. The Survival of the Fittest. This expression was first used by the famous British philosopher Herbert Spencer and later adopted by Darwin. As Darwin pointed out, the word fittest has no moral connotation, but means simply the degree of adaptation of the organism to its environ-

ment. For example, in a desert plant the individuals with best drought-resisting tissues are most fit, other things being equal In animals, fitness may depend upon a variety of characteristics, such as speed, strength, weapons, defensive armor, well-developed sense organs, intelligence, and (among the most important of all) resistance to invading parasites In man, in modern times, fitness depends much more on the two traits last mentioned than on the first two

As Darwin himself pointed out, the real meaning of the survival of the fittest from the evolutionary standpoint is not merely the survival of the individual but rather the relative numbers of different types of offspring produced which themselves reach the age of reproduction. A failure to reproduce is just as effective in selection as elimination by death Other things being equal, those individuals, types, and races with the highest rates of reproduction tend to replace those with lower rates

In the struggle for existence, chance, as we all know, plays a part But in the long run chance cancels out, and those individuals which are best fitted to the environment survive in larger numbers than those not so well fitted The surviving individuals are therefore naturally selected, and in so far as their differences from those that perish are hereditary, they will tend to transmit these differences to the next generation If this process is continued over many generations the result, according to Darwin, may be a new species In "The Origin of Species" he illustrates the principle in the case of the giraffe in the following words.

The giraffe, by its lofty stature, much elongated neck, fore legs, head and tongue, has its whole frame beautifully adapted for browsing on the higher branches of trees [see Fig. 70, p 209] It can thus obtain food beyond the reach of the other Ungulata or hoofed animals inhabiting the same country; and this must be a great advantage to it during dearths. . . . So under nature with the nascent giraffe, the individuals which were the highest browsers and were able during dearths to reach even an inch or two above the others, will often have been preserved; for they will have roamed over the whole country in search of food. That the individuals of the same species often differ slightly in the relative lengths of all their parts may be seen in many works of natural history, in which careful measurements are given These slight proportional differences, due to the laws of growth and variation, are not of the slightest use or importance to most species But it will have been otherwise with the nascent giraffe, considering its probable habits of life; for those individuals which had some one part or several parts of their bodies rather more elongated than usual, would generally have survived. These will have intercrossed and left offspring, either inheriting the same bodily peculiarities, or with a tendency to vary again in the same manner, while the individuals less favored in the same respects will have been the most liable to perish.

We see here that there is no need to separate single pairs, as man does, when

he methodically improves a breed, natural selection will preserve and thus separate all the superior individuals, allowing them freely to intercross, and will destroy all the inferior individuals. By this process long-continued, which exactly corresponds with what I have called unconscious selection by man, combined, no doubt, in a most important manner with the inherited effects of the increased use of parts, it seems to me almost certain that an ordinary hoofed quadruped might be converted into a giraffe.

Notice that Darwin here combines, in the last sentence, the theory of natural selection with the now discredited hypothesis of the inheritance of the effects of use.

The process of natural selection is evidently similar to the method practiced by man in improving his domesticated animals and plants, if instead of selection by a human agency we substitute selection by the forces of nature. As an example of man's power of directing the adaptation of animals to particular functions let us compare two widely used breeds of horses—the Belgian, a draft breed, and the thoroughbred, a breed used for running races. The former (Fig. 101) was developed on the continent of Europe, the latter in England. The Belgian was probably derived from the wild horses of Europe which existed down into medieval times. From all the available evidence these wild horses were much smaller and lighter in weight than the Belgian, although in western Europe there existed a forest type of wild horse with large bones and feet. During the Middle Ages the heavy horse was bred for riding, since such a type was required to carry a knight in full armor. Later, horses were used for pulling heavy loads, and here again size and strength were most important. The Belgian is among the heaviest of modern breeds. Stallions commonly weigh from 2,000 to 2,500 pounds. The body is broad, deep, and heavily muscled, and the legs are short and strong. The neck is short and heavily arched. The height is about 17 hands, or 68 inches. The Belgian illustrates well what can be done by man in modifying an animal in a specific direction. The contrast between the Belgian and the thoroughbred (Fig. 102) is striking. Here the whole force of selection has been directed toward increased speed. Stallions that have outstanding records on the track are retired after a few years to the stud where they often continue to sire colts for many years. Selection of females that are of superior speed likewise is practiced. As mentioned above, the thoroughbred was developed in England for the specific purpose of racing. Its ancestry is a mixture of native English horses crossed with horses imported from Arabia, Turkey, and North Africa about 1700. By combining the good qualities of both types the size and speed of the breed were increased, until today the average height is about 16 hands and the speed superior to that of the Arabian. The Arabian is about 15 hands, and the

original English running horses were still smaller. Thoroughbreds are about half the weight of the Belgian.

The thoroughbred apparently now closely approaches its maximum speed under present methods of training and riding. The Kentucky Derby record is held by Whirlaway (2·01 $\frac{2}{5}$, 1941), which was only $\frac{2}{5}$ second faster than the time of Twenty Grand (Fig. 102) in 1931. The best thoroughbreds today show striking uniformity of body build, evidence of intensive selection for a type adapted for speed. New mutations

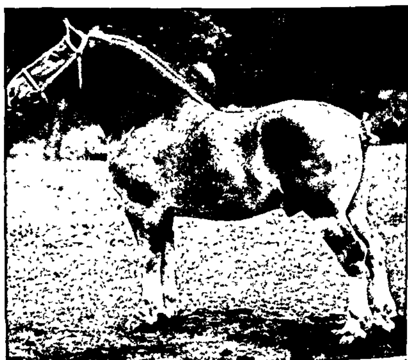


Figure 101. Prize-winning Belgian stallion, representative of a breed especially adapted for pulling heavy loads. Compare the heavily muscled and relatively short and thick body, neck, and legs with the slender proportions of the race horse shown in Fig 102 Tail cropped and tied with ribbon. (*Photo by J. F. Abernathy Live Stock Photo Co., Chicago*)

or some improved method of training may, of course, lead to further advance.

EFFECT OF NATURAL SELECTION ON MAN

Natural selection probably operates in all species, including man. In spite of this we shall no doubt always have a certain proportion of defective and diseased persons in the population who owe their misfortune to heredity. Even though the defect or disease kills its possessor before the reproductive age is reached, the injurious gene will probably reappear by mutation.

Let us first consider a population in which there is present a sex-linked recessive gene that either kills all affected persons, males as well as females, prior to the age of reproduction, or prevents them from having children. The reproductive fitness of affected persons is therefore zero. In such a population, in the absence of migration, the frequency of the

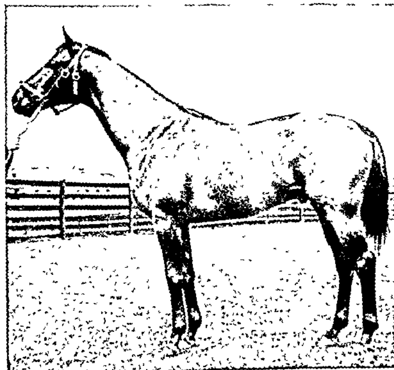


Figure 102. Thoroughbred stallion, Kentucky Derby winner Twenty Grand, as a four-year-old. Note how in every way the body is admirably adapted for speed: long slender neck and legs, small feet, deep chest, thin flanks, and well-muscled thighs and shoulders. (*From Estes and Palmer, An Introduction to the Thoroughbred Horse, The Blood-Horse,* 1942.)

trait will decline by 50 per cent in each generation, provided there are no new mutations to or from the recessive gene and provided that heterozygous women have on the average the same number of children as women who are free from the gene. At this rate of depletion not many generations are needed to reduce the frequency of the gene to an infinitesimal percentage.

As a concrete example of the way this process of reduction goes on, let us start with a population (generation I) in which one female in 5,000

is heterozygous for a sex-linked lethal gene (a). Since each female has two X chromosomes, one X chromosome in 10,000 chromosomes carries gene a All males are of genotype A, since only these survive. Hence in generation II only one female (as well as one male) in 10,000 will receive a defective gene, and this recessive gene will come from her mother. Thus in one generation the frequency of the gene in females has been reduced from one in 10,000 to one in 20,000 Consequently, the proportion of affected males produced by these women in the next generation will be one in 20 000—a reduction of the trait by 50 per cent in one generation Summarizing the argument, we have:

	Females	Males
Generation I	1 Aa: 4,999 AA	All A
Eggs from I	1 a: 9,999 A	Sperms from I all A
Generation II	1 Aa: 9,999 AA	1 a(dies): 9,999 A
Eggs from II	1 a·19,999 A	Sperms from II all A
Generation III	1 Aa.19,999 AA	1 a(dies): 19,999 A

It is obvious that under the foregoing conditions a sex-linked recessive gene will in a few generations become practically extinct. If for a given deleterious trait there is no apparent reduction in frequency, a natural explanation is that new mutations occur often enough to balance the losses. In our supposed case a mutation rate of one for each 30,000 X chromosomes per generation (combining males and females), beginning with generation I, will just balance the losses resulting from the elimination of affected males The gene frequency is then said to be at equilibrium We may now state as a general conclusion that *a sex-linked, recessive, lethal gene is at equilibrium frequency when the net mutation rate to it per generation per X chromosome is one-third the rate of production of affected males.*

Where the sex-linked gene is not fully lethal, as in hemophilia, the actual mutation rate at equilibrium will naturally be somewhat less than one-third of the frequency of affected males. Some hemophilic males do live to reproduce. Estimates of their reproductive fitness (considering fitness as their fecundity compared to that of normal males) have been made by several investigators Haldane[1] estimates their fitness at about 30 per cent; hence loss of fitness is 70 per cent. In order to calculate the mutation rate necessary to balance selection against the gene for hemophilia we merely multiply the mutation rate that would be needed to balance a full lethal by the percentage loss of fitness. For example, taking Andreassen's estimate for the frequency at birth of hemophilic males in

[1] J. B. S Haldane, The Rate of Mutation of Human Genes, *Proc. 8th Intern Congr. Genet*, edited by Gert Bonnier and Robert Larsson (*Hereditas* suppl vol), 1949.

Denmark (0.00013) and Haldane's estimate of the loss of reproductive fitness of hemophilics (0.70), we obtain 0.00013 × ⅓ (rate of mutation necessary to balance a full lethal) × 0.70 = 0.00003 as the estimated rate of mutation of the normal gene to the gene for hemophilia in Denmark.

In the foregoing discussion we have assumed that heterozygous females produce no more offspring than homozygous dominant females. If for any reason, however, heterozygous females have a higher rate of reproduction, the proportion of affected males might be maintained in the absence of new mutations, in spite of selective elimination of affected males.

CHANGES IN GENE FREQUENCY

The case of hemophilia in man suggests that changes in the frequencies of genes constitute the basic process in evolutionary change. In studying evolution today, therefore, attention is centered upon all factors that may have an effect upon gene frequencies within a population. These factors are (1) mutation, (2) selection, (3) differential migration to the population, and (4) accidental elimination (important where the size of the population is small). The word *mutation* is here used in the comprehensive sense to include changes in the gene as well as chromosome changes. *Selection* includes differential mating, differential fecundity, differential viability at all ages, and differential emigration. The effect on the population is the same whether a particular genotype tends to die, to be infertile, or to emigrate more than others. *Immigration* has essentially the same effect as recurrent mutation. It can, for example, introduce a gene into a population that lacks it. Emigration cannot do this and is in effect merely one of the many kinds of selection, that is, processes that change gene frequency without change of the hereditary material itself (mutation) or introduction from without (immigration). Emigration can change gene frequency in the population only if two or more alleles are already present.

Two factors which are sometimes mentioned as important but which in themselves have no effect upon change in gene frequency are (1) the existing frequencies of the alleles of a gene and (2) dominance. The truth of this last assertion will be brought out in the following section.

THE HARDY-WEINBERG LAW

In a large population of bisexual organisms in which breeding is at random with respect to a particular pair of alleles there is no tendency for the frequency of either allele to change at the expense of the other—provided of course that there is no mutation, selection, or differential migration or mating with respect to this pair of alleles.

Example 1. Let us take first the simplest case, one in which in a large population breeding at random with respect to a given pair of alleles, A and a, the frequency of each allele is 50 per cent. In this population one-half of the eggs as well as sperms produced will be A and one-half a The most probable combinations of these in the zygotes according to Mendel's first law will be $(\frac{1}{2} A + \frac{1}{2} a)^2 = \frac{1}{4} AA + \frac{1}{2} Aa + \frac{1}{4} aa$ The frequencies of the alleles A and a obviously remain at 50 per cent each

Let these individuals now mate at random. The resulting matings may be found by the use of a checkerboard of nine squares or by the fractional method

$$\left(\tfrac{1}{4} AA + \tfrac{1}{2} Aa + \tfrac{1}{4} aa\right)^2 =$$

9 possible matings	*Offspring of 9 matings*		
$\frac{1}{16}$ $AA \times AA$	$\frac{1}{16}$ AA		
$\frac{1}{8}$ $AA \times Aa$	$\frac{1}{16}$ AA	$\frac{1}{16}$ Aa	
$\frac{1}{8}$ $Aa \times AA$	$\frac{1}{16}$ AA	$\frac{1}{16}$ Aa	
$\frac{1}{16}$ $AA \times aa$		$\frac{1}{16}$ Aa	
$\frac{1}{4}$ $Aa \times Aa$	$\frac{1}{16}$ AA	$\frac{1}{8}$ Aa	$\frac{1}{16}$ aa
$\frac{1}{16}$ $aa \times AA$		$\frac{1}{16}$ Aa	
$\frac{1}{8}$ $Aa \times aa$		$\frac{1}{16}$ Aa	$\frac{1}{16}$ aa
$\frac{1}{8}$ $aa \times Aa$		$\frac{1}{16}$ Aa	$\frac{1}{16}$ aa
$\frac{1}{16}$ $aa \times aa$			$\frac{1}{16}$ aa
Summation of like genotypes	$\frac{1}{4}$ AA +	$\frac{1}{2}$ Aa +	$\frac{1}{4}$ aa

Again the gene frequencies have not changed, but persist at $\frac{1}{2} A : \frac{1}{2} a$

Example 2. The same rule applies if we start with alleles in *unequal* frequency For example, if we select any frequencies at random, so long as their sum = 100 per cent, say, A = 70 per cent, and a = 30 per cent, the offspring are found as above by squaring the binomial,

$$(0\ 7\ A + 0\ 3\ a)^2 = 49 \text{ per cent } AA + 42 \text{ per cent } Aa + 9 \text{ per cent } aa$$

Adding up the genes $(49 + 42/2)\ A + (9 + 42/2)\ a$, we get 70 per cent A: 30 per cent a, the same as in the beginning. Carrying out the nine possible matings as in Example 1 will likewise show no change in gene frequencies in the subsequent generation

Since the rule applies whatever the frequencies of the alleles, it is commonly expressed thus· If p equals the frequency of A, and q equals the frequency of its allele a, the frequencies of the genotypes in each generation equal $(p\,A + q\,a)^2 = p^2\,AA + 2\,pq\,Aa + q^2\,aa$ There is thus no tendency of the frequencies to change from generation to generation under the conditions as stated The rule applies whether Aa represents a dominant type or an intermediate; therefore dominance as such is not a factor in changing gene frequency

The rule was first clearly stated by G. H Hardy and W. Weinberg, in-

dependently, in 1908, hence has come to be known as the Hardy-Weinberg law

VARIATIONS CLASSIFIED AS TO THEIR EFFECTS

Hereditary variations are of three types so far as fitness is concerned, namely, good, bad, and indifferent Observation shows that the most frequent type is the bad variation, i e , the one making the organism less fit. The least frequent type is the good variation, which increases the fitness Completely indifferent mutations are probably very rare, owing to the tendency of genes to have manifold effects, the conspicuous effect may be indifferent while the concealed effects may be either good or bad The tendency for most mutations to be injurious may come as a shock to one who has given it no thought, and he may wonder how any species can survive for long under such conditions Selection is the answer Some selection is necessary in order to prevent deterioration, while rigorous selection is necessary in order to obtain positive improvement Every plant and animal breeder is familiar with this fact and acts accordingly

Sewall Wright has pointed out that indifference as the effect of a mutation is merely a boundary between good and bad in average effect on selective value, and thus probably never occurs in a strict sense, that the real difficulty in classification comes from the probability that all mutations with minor effects (and some with major effects) are good in some combinations, bad in others, and that such mutations are probably almost always bad when they first occur, but if carried in the population at low frequency, some of them may come to be good, at least locally, as the prevailing genotypes change He has emphasized that selection relates to total génotype, not to genes, and thinks that there is no necessity that there be any initially beneficial genes to permit evolution to occur

In nature, the organism is always surrounded by environmental factors ready to remove those individuals that are least adapted or to inhibit their reproduction These factors include predators, parasites, adverse climatic conditions, competition within the species, and so on Without such selective factors we can see no means of preventing the deterioration of the species as a whole. The occasional potentially beneficial mutation is the starting point of evolution to a higher level of adaptation. New things are added in this way

Heretofore we have emphasized the concept that biological fitness (adaptation) has meaning only in relation to the environment in which the organism lives What is fit in one environment may well be deleterious in another. This principle seems to find an illustration in an inherited characteristic of the human blood found with high frequency in certain areas where malaria is unusually prevalent

BALANCED POLYMORPHISM—SICKLE-CELL DISEASE

In 1910 Professor J. B Herrick of Rush Medical College, Chicago, found in the blood of an American Negro student who suffered from chronic anemia red blood corpuscles of peculiar shapes. Many of the corpuscles were elongated and some were curved like a sickle; the latter he called sickle cells (Fig 103) The disease became known as sickle-cell anemia, or sickle-cell disease.

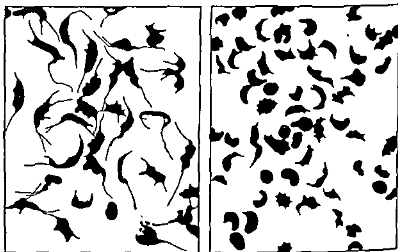


Figure 103. Red blood cells of persons with sickle-cell anemia and sickle-cell trait (*From Singer, The Sickle Cell Trait in Africa, Am. Anthropologist*, 55.631–648, 1953 *Drawings by Mary E McCarthy, Carnegie Institution of Washington, Department of Embryology.*)

In 1923 W. H Tallaferro and J. G. Huck, of the University of Chicago, showed that sickle-cell disease is inherited as a simple Mendelian characteristic A double dose of the mutant gene is required for the development of the symptoms, the heterozygote shows no pathological symptoms, but can be diagnosed by an examination of the blood (Fig 103). Heterozygous carriers of the gene are said to have the sickle-cell trait.

Numerous investigators have studied the genetics and pathology of sickle-cell disease, and from their findings the following conclusions may be abstracted The gene *Sk* responsible for the sickling causes the production of a special kind of hemoglobin known as hemoglobin S Hemoglobin S is precipitated when freed of its oxygen. This precipitation causes the red corpuscles to assume their peculiar shapes In the heterozygote, *Sk sk*, about 60 per cent of the hemoglobin is normal and 40 per cent is hemoglobin S; with this mixture the corpuscles show a mild degree of abnormality. In the homozygote, *Sk Sk*, practically all of the hemoglo-

bin is of the abnormal type, and at oxygen tensions of venous blood the corpuscles develop filamentous processes These highly abnormal corpuscles tend to form clumps and clog the smaller blood vessels The disturbed circulation leads to a variety of symptoms retardation of physical development and crises with severe pain in the abdomen, back, head, and extremities There may be enlargement of the heart and atrophy of brain cells The abnormal corpuscles are rapidly destroyed in the body, with the resulting anemia Persons with sickle-cell disease suffer from a very high death rate.

As mentioned earlier, the heterozygotes, who possess the sickle-cell trait, exhibit no important pathological symptoms and can be detected only by a microscopic examination of the blood The test is carried out by sealing a drop of blood under a cover slip with petrolatum After a day or two the oxygen tension in the corpuscles is reduced to the point at which sickling occurs The sickling may be speeded up by the use of a reducing agent such as ascorbic acid in a 4 per cent solution

The gene for sickle-cell disease seems not to have been found in persons of North European ancestry nor in Mongoloids It is widespread among the tribes of tropical Africa and has been found among certain primitive tribes in southern India and among some European Caucasoids bordering the Mediterranean Sea About 9 per cent of American Negroes show the sickle-cell trait and are therefore heterozygous for the gene

Assuming that the heterozygote suffers no handicap with respect to survival or reproduction it is possible to calculate the expected frequency of sickle-cell disease in a population Among American Negroes, if mating is at random with respect to the sickle-cell trait, 9 per cent of 9 per cent, or 0 81 per cent, of marriages should be between two heterozygotes The children of two heterozygotes run a risk of one in four of developing sickle-cell disease Ignoring the very few children produced by persons who have sickle-cell disease (homozygotes), it is evident that 25 per cent of 0 81 per cent, or 0 2025 per cent, of Negro children in the United States are expected to be homozygous for the sickle-cell gene The number of affected persons observed clinically agrees fairly well with the calculated number—about one in 500

Recent estimates indicate that the ancestry of American Negroes as a group is about two-thirds African and one-third Caucasoid and American Indian. Numerous studies made in West Africa, ancestral homeland of most American Negroes, show that about 20 per cent of the natives have the sickle-cell trait Reliable estimates of the frequency of sickle-cell disease in the same region are not available Calculations as above indicate that about 1 per cent of births should be homozygous for the gene.

A C. Allison,[1] of the Radcliffe Infirmary, Oxford, England, has made

[1] A. C. Allison, Notes on Sickle-cell Polymorphism, *Ann. Human Genet*, 19:39–57, 1954.

clinical studies of the Luo tribe in East Africa. He concludes that only rarely do individuals who are homozygous for the sickle-cell gene reach adult life and have children J. V Neel, of the Heredity Clinic, University of Michigan, estimates that the fertility of individuals with sickle-cell disease in this country is 20 per cent of normal.

With such severe natural selection against the gene how are we to account for its present high frequency among the tribes of tropical Africa? One possibility is the frequent mutation of the normal gene to the sickle-cell gene If the gene frequency remains constant in a population, the new mutations must equal the genes lost through selection against the homozygote—provided that the heterozygote has the same selective advantage as the homozygous normal Considering the existing frequency of the sickle-cell gene among many African tribes, it is highly improbable that new mutations can account for the losses due to adverse selection. a rate of about one mutation per hundred gametes per generation would be needed to balance the losses, no such mutation rate has been observed in man Furthermore, if the mutation rate is high, why has no mutation to the gene been discovered among North Europeans and Mongoloids? We therefore ought to consider the possibility that the heterozygote has a selective advantage over the homozygous normal. Allison has produced evidence for just such an advantage He finds that individuals who have the sickle-cell trait display a much higher resistance to subtertian malaria than do those without the trait; that in areas of hyperendemic malaria the children with sickle-cell trait survive in larger proportions than do those without it This differential survival tends to increase the frequency of the sickle-cell gene, and the more severe the malaria the greater is this effect But as the sickle-cell gene increases in frequency, the number of persons dying of sickle-cell disease also increases The result is a balance, or equilibrium, between the losses of the normal gene through malaria and the losses of the sickle-cell gene through sickle-cell disease This interesting case is an example of *balanced polymorphism* It is also an example of one form of heterosis. or hybrid vigor, known as overdominance, and illustrates the fact that the concept of fitness is always related to the environment· in a country free of malaria the heterozygote is not more fit than the normal homozygote

Among 35 East African tribes Allison found that the incidence of the sickle-cell trait was invariably above 10 per cent in tribes suffering from hyperendemic malaria and less than 10 per cent in tribes living in areas where malaria was absent or only epidemic. He notes that in Africa, Greece, and southern India the sickle-cell trait attains high frequencies only in regions where subtertian malaria is transmitted during several months of the year.

Returning to the United States, how can we account for the fact that

the sickle-cell trait is present in only about 9 per cent of American Negroes as compared with 20 per cent in the natives of West Africa? The difference seems too great to depend entirely upon the one-third Caucasoid and American Indian genes in the Negro population More probably the selective effect of malaria in the United States has been insufficient to maintain the higher frequency of the sickle-cell gene against its constant depletion through sickle-cell disease Although malaria was formerly a very serious problem in this country, in recent years it has accounted for less than 100 deaths annually in the entire United States, exclusive of armed forces overseas It seems safe to predict that the frequency of sickle-cell disease among American Negroes will continue to decline through the force of natural selection

Let us now attempt to summarize the theory of natural selection in modern genetical terms In doing so it will be noticed that the only significant changes from Darwin's statement of the theory are the elimination of the hypothesis of the inheritance of acquired characters and the addition of the contributions of Mendelian genetics, including the gene theory.

SUMMARY OF THE THEORY OF NATURAL SELECTION

1. As a consequence of the overproduction of offspring, hereditary variation, and the struggle for existence, there is in each generation a tendency toward the differential survival of the better-adapted (fittest) individuals.

2 Hereditary variations are known to result from

a. Segregation, assortment, and *recombination* of hereditary factors already present in the organism

b Mutation, using this term to include changes in minute localized regions of the chromosomes (gene mutations) as well as gross changes such as additions or subtractions of whole chromosomes or chromosome sets, or of gross reorganizations of chromosomes. Both types of mutations can be induced by the use of penetrating radiations and by certain chemicals, e g , mustard gas

3 Owing to the differential survival of the better-adapted individuals there is a selection of hereditary factors that condition such adapted individuals If the selection goes systematically in one general direction, as it might under the influence of a steady change in the environment, there will result a gradual shift in the relative frequencies of alternative characteristics and of the associated hereditary factors. Two well-known examples in insects are:

a. Increase in relative frequencies of dark-colored (melanic) varieties of certain moths in the neighborhood of smoky industrial cities in recent

years The dark color is considered an example of protective coloration; it is due to a dominant gene.

b Increase of a resistant race of red scale insects in citrus groves of California, subjected to hydrocyanic acid gas fumigation, at the expense of the susceptible strain The difference between the two races of red scale insect is due to a single sex-linked gene. The heterozygote is intermediate in resistance

4. The selective process may continue until a character that was once rare predominates or even replaces its alternatives

5 Since selection involves many characters of the organism, a new assortment of characters may in time come to distinguish the species

6. Distinct species, even those most like each other, usually show numerous distinguishing characters, and these do not differ in kind from characters which distinguish subspecies of a single species.

Conclusion. If the foregoing statements are accepted as true, it follows that a species may in time come to possess a combination of characteristics sufficient in number and grade to warrant its designation as a new species, even though the original species has not been split up into isolated groups The original species has been gradually replaced by a new species

Where a species becomes split up into isolated groups by barriers, differential selection within the separated groups may lead to the origin of one or more new species this is an illustration of divergence.

SEXUAL SELECTION

In "The Origin of Species" Darwin discussed briefly a special case under natural selection which he called sexual selection. This was developed in great detail in one of his later books, "The Descent of Man and Selection in Relation to Sex." Quoting from the former work:

> This form of selection depends, not on a struggle for existence in relation to other organic beings or to external conditions, but on a struggle between the individuals of one sex, generally the males, for the possession of the other sex The result is not death to the unsuccessful competitor, but few or no offspring Sexual selection is, therefore, less rigorous than natural selection Generally, the most vigorous males, those which are best fitted for their places in nature, will leave most progeny. But in many cases victory depends not so much on general vigor, as on having special weapons, confined to the male sex. A hornless stag or spurless cock would have a poor chance of leaving numerous offspring . . .
>
> Among birds, the contest is often of a more peaceful character All those who have attended to the subject, believe that there is the severest rivalry between the males of many species to attract, by singing, the females The rockthrush of Guiana, birds of paradise, and some others, congregate, and successive males display with the most elaborate care, and show off in the best manner, their gorgeous

plumage, they likewise perform strange antics before the females, which, standing by as spectators, at last choose the most attractive partner Those who have closely attended to birds in confinement well know that they often take individual preferences and dislikes

Thus it is, as I believe, that when the males and females of any animal have the same general habits of life, but differ in structure, color, or ornament, such differences have been mainly caused by sexual selection that is, by individual males having had, in successive generations, some slight advantage over other males, in their weapons, means of defense, or charms, which they have transmitted to their male offspring alone .

Among many species of birds and mammals in which the males fight for the possession of the females, polygamy is the rule, and since the sex ratio is usually close to 1 1 this means that the defeated males are deprived of mates, leaving the more vigorous males to become the sires of the next generation. The effectiveness of this type of selection cannot well be denied.

There has been much debate over the second type of sexual selection as stated by Darwin, namely, the active selection of mates by one sex or the other. It is generally admitted that such secondary sexual characters in animals as brilliant colors, elaborate ornaments, and complex behavior patterns displayed during courtship serve as a stimulant to mating For some species evidence has accumulated in recent years showing that the females discriminate with respect to sexual displays of the male [1]

With man there seems little doubt that the active choice of mates, by females as well as males, has been an important factor in the origin and evolution of the various human types This kind of selection seems to offer the greatest possibilities for the continued improvement of mankind.

ISOLATION AS A FACTOR IN EVOLUTION

From the foregoing discussion it is evident that a species may gradually change under the impact of natural selection until it comes to be something quite different from the original If the species is a single unit, with perfectly free opportunities for interbreeding among all the individuals of the species, any new advantageous characteristic that arises may spread throughout the population, thus the whole species will change as a unit, without a multiplication of species A study of the two great kingdoms, the plant kingdom and the animal kingdom, convinces us that most species have arisen as a result of splitting up of preexisting species. There is no other explanation of the complex branching relationships

[1] D J Merrill, Selective Mating in *Drosophila melanogaster*, *Genetics*, **34**:370–389, 1949.

found in these two kingdoms. How are we to explain this splitting up of species? The answer is the presence of some factor which prevents free and random mating. This factor is isolation

There are two principal types of isolation. *geographical isolation* and *reproductive isolation* In the former, the species is divided into two or more subgroups by physical barriers so that communication between the groups is difficult or impossible For example, for a long period of time the marine animals of the Caribbean Sea and those of the Pacific Ocean were free to migrate back and forth through a neck of water which extended across what is now the Isthmus of Panama. Later, during the Pleistocene epoch, the land was elevated, forming a continuous land bridge between North and South America and cutting off means of communication As a result, the marine animals on the two sides of the isthmus gradually diverged until many of them became distinct species, although separated by only a few miles. Among the fishes the species today usually occur in related pairs, one on either side of the isthmus Numerous similar examples could be given for animals as well as for plants

Barriers to migration such as mountain ranges, deserts, and oceans undoubtedly played an important role in the production of the major divisions and races of mankind Wright[1] has recently developed the theory that *distance* alone may constitute an effective isolating agency in the origin of races Among human beings the tendency today is obviously toward the breaking down of such barriers through the improvement of modes of transportation, accompanied by a reduction in the cost of travel. Whether there finally comes an amalgamation of all the races into one is doubtful, however, because of the strength of the second type of isolation —reproductive isolation

Under reproductive isolation we should include, in the higher animals and man, psychological isolation. Reproductive isolation may cause groups living in the same region to remain distinct even though there is no physical barrier to prevent their mixing, as sometimes happens to a certain extent among the major races of man If mating occurs between certain species of animals, the offspring may be few, nonviable, weak, or sterile. There is no evidence of any such effect among human races This is one reason for classifying all human beings as members of a single species

When two groups are isolated, whatever the means, they gradually tend to diverge. This follows partly as a result of natural selection operating somewhat differently in the two groups. Adaptive differences may thus be accounted for; but nonadaptive characters require a different explanation.

[1] Sewall Wright, Isolation by Distance, *Genetics*, 28:114–138, 1943.

THE ORIGIN OF NONADAPTIVE DIFFERENCES

Adaptive characteristics have always claimed the major attention of students of evolution, but it is also recognized that probably every species and subspecies have certain distinguishing characteristics that have had no selective value. Natural selection has no power to increase or to decrease the frequency of such characteristics How then have they become a fixed part of populations?

During the latter part of the last century various attempts were made to account for evolution in the absence of selection by postulating an innate force or tendency within the organism causing it to evolve along some particular line, more or less irrespectively of the external conditions The botanist Nageli was one of those who held such views, and there were other biologists and some paleontologists with similar hypotheses, sometimes associated with a belief in the inheritance of acquired characters To these theories the term *orthogenesis* (straight origin) has been applied.

As pointed out in our discussion of mutation in Chap 12, there are limitations to the directions in which mutations may go, set by the nature of the organism itself To this extent there is an inherent directing force within the organism But since in all species studied intensively there has been found a great variety of mutations affecting all parts of the body, the exact course of evolution must be directed by forces outside the organism Orthogenesis as a theory of evolution is therefore no longer seriously considered by most students of the problem of evolution

Darwin recognized the existence of nonadaptive characteristics although he regarded them as less numerous than did many of his contemporaries Some of the alleged cases he ascribed to our ignorance of the uses to which many structures may be put by the possessor For example, unless one knew something of the mode of reproduction in seed plants and the part played by insects in the pollination of flowers, he would not be able to see any advantage to the plant in the beautiful colors and complex structures of flowers.

Many cases of nonadaptive differences were attributed by Darwin to "correlated variation." By this he meant that a change produced in one part of the organism was often accompanied by changes in other parts, due to interactions in growth and development As an example he refers to the fact that white cats with blue eyes are usually deaf. We would today class such cases under the head of multiple effects of a single gene (Chap. 6), since we know that in cats the character white with blue eyes is a Mendelian dominant over colored normal; deafness develops in homozygous animals.

There are probably many genuine cases of nonadaptive differences Applying the known principles of heredity, including the mechanism of hereditary changes by mutation and chromosome changes, we are now able to give a fairly simple explanation of such cases

Imagine a species from which a small group is split off by some sort of barrier Because of repeated mutations, segregation, and assortment no species is ever made up of absolutely identical individuals. The two groups will therefore differ somewhat in the frequency of certain nonadaptive genes Following the split, each group will breed only among its own members, thus preserving such original differences. If a separated group is quite small, so that inbreeding takes place, some nonadaptive genes will be preserved and others eliminated merely as the result of chance. The experiments on inbreeding in guinea pigs, described in an earlier chapter, constitute a good demonstration of how this occurs under extremely close inbreeding With inbreeding of a less extreme type the same effect follows, but more slowly.

Mutations will of course continue to occur in each group, but will not follow identical patterns in both; for, as we have seen, mutation is to a certain extent a random matter. This will increase still further the differences between the groups Thus by the chance distribution of genes, one group comes gradually to differ from the other group in nonadaptive characteristics

It is probable that some of the nonadaptive differences that distinguish the modern races of mankind have arisen in the manner just described, although of course some of these differences, such as hair form, thickness of lips, and facial features, may have arisen in part through sexual selection.

HYBRIDIZATION AND THE ORIGIN OF SPECIES

There is much evidence that many new species of plants have arisen suddenly in nature as a result of the chance crossing of two distinct species The new species thus produced are polyploids and contain all of the chromosomes of both original species.

Within recent years, taking advantage of the newer knowledge of genetics, experimenters have been able to produce by hybridization synthetic new species of plants which meet all the tests of separate species in nature. Thus the criticism, formerly leveled at biologists, to the effect that if new species originate in nature under natural forces, experimenters should be able to duplicate the process in the laboratory, has been finally answered. The following example will illustrate the method.

Successful crosses have frequently been made between the radish and cabbage. These two plants belong to distinct species and are not even

members of the same genus, although they are distantly related Each is a diploid with nine pairs of chromosomes (Fig 104) The hybrid also has 18 chromosomes, 9 derived from the radish and 9 from the cabbage The F_1 hybrid is usually sterile, but occasionally produces seeds The F_2 plants raised from such hybrid seeds are variable, in accordance with the

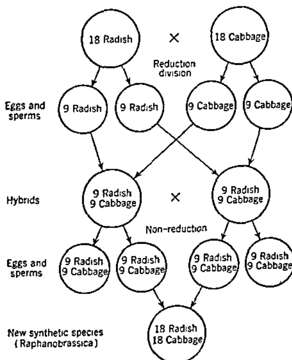


Figure 104. Diagram showing distribution of the chromosomes in the crossing of the radish (*Raphanus sativus*) with the cabbage (*Brassica oleracea*) resulting in the experimental creation of the distinct new species (*Raphanobrassica*) (Each original species has 18 chromosomes)

general rule of variability in the offspring of hybrids Some of these F_2 offspring which resemble their hybrid parents are entirely fertile; furthermore, unlike ordinary diploid hybrids, they breed true to type. When their cells are examined they are found to possess 36 chromosomes, just twice the number in their hybrid parents and in the original cabbage and radish ancestors

The explanation of this result lies in the failure of the reproductive cells in the F_1 hybrid to undergo a reduction division, thus leaving the eggs and sperms with 18 chromosomes each instead of the usual 9 Of

the 18 chromosomes in the eggs and sperms, 9 make up the entire cabbage set and the other 9 make up the entire radish set. At fertilization, therefore, each fertilized egg contains two sets of radish chromosomes and two sets of cabbage chromosomes. During the development of the plant from the fertilized egg, each cell in the body receives, as a result of mitosis, the full double set of both cabbage and radish chromosomes Thus there has been established by the process of hybridization a new tetraploid species containing in its cells all the genes of both original species The synthetic species shows the type of reproductive isolation which is expected in a distinct species only rarely is a cross to the original parents successful, and the few offspring obtained are usually sterile.

Although in gene make-up the new synthetic species is the simple sum of the two original species, this is not true as to its visible characters Some of its characters are intermediate between the cabbage and the radish, some resemble one parent or the other; and some are peculiar to the new species For example, the leaves resemble the radish and the root system resembles the cabbage. It is, therefore, of no value commercially. The seed pod (Fig. 105) is intermediate in structure. As illustrated in the drawings, the seed pod of the radish is spindle-shaped, of one piece, and nondehiscent, i.e , it does not burst open to release the seeds The long seed pod of the cabbage is made up of two valves and is dehiscent At the base of the radish pod is a small structure considered homologous to the two valves of the cabbage pod, while the tip of the cabbage pod is homologous to that of the radish The F_1 hybrid and the F_2 tetraploid obviously combine the single structure of the radish at the tip with the double-valve structure of the cabbage at the base. The triploid, pentaploid, and hexaploid show various combinations of these traits, as might be expected from their chromosome make-up

In addition to large seed pods with many seeds, the tetraploid *Raphanobrassica* has a large and vigorous plant body characteristic of tetraploids in general. Its cells also are large. Other examples similar to the radish-cabbage case are described by Professor Stebbins in a comprehensive volume.[1]

The evidence is convincing that nature has frequently performed experiments similar to the man-made experiments just described and that new wild species, especially among plants, have frequently come into existence in this way. Numerous examples are given by Stebbins and by Clausen et al. (footnote, page 239). Several species of wild plants have been resynthesized by crossing their supposed original ancestors

The economic importance of the production of polyploids through hybridization should be emphasized This is a new and growing field But

[1] G Ledyard Stebbins, Jr., "Variation and Evolution in Plants," Columbia University Press, New York, 1950

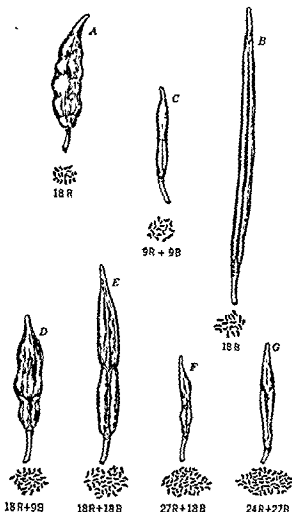


Figure 105. Seed pods and chromosomes. (*A*) Radish (*B*) Cabbage. (*C*) F_1 diploid hybrid between radish and cabbage (*D*) Triploid from a cross of *A* and *C* (*E*) Tetraploid *Raphanobrassica*, obtained by self-pollination of *C* (*F*) Pentaploid from a cross of *A* and *C* (*G*) Hexaploid, somewhat deficient in radish chromosomes (*From Sharp, "Introduction to Cytology," McGraw-Hill Book Company, Inc., after Karpechenko.*)

already, improved domesticated fruits and ornamental plants have been produced, a recent interesting book by two British authors[1] cites numerous examples of these.

In the higher animals very few examples suggesting the origin of polyploid species by hybridization have been found. Two chief reasons are given for this difference between plants and animals: in the first place the great majority of animals show a strong preference for mating with members of their own species, secondly, a new polyploid species can be founded more readily in an organism that is hermaphroditic, especially

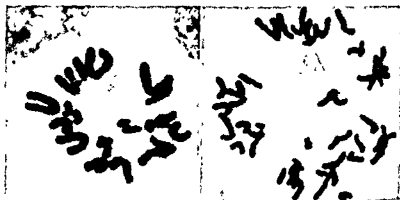


Figure 106. Microphotographs of spermatogonial cells in the testes of two species of hamster. *Left: Cricetulus griseus* (Striped hamster), $2n = 22$ *Right: Mesocricetus auratus* (Golden hamster), $2n = 44$ $\times$ 2,000 (*From Sachs, Heredity,* 6.357–364, 1952.)

if it is self-fertilizing, than in one with separate sexes The great majority of plant species are hermaphroditic, while most animals are bisexual

In bisexual species sex is commonly determined by the sex chromosomes As we have seen in an earlier chapter these may occur as XO in one sex and XX in the other, or as XY in one sex and XX in the other In the former case polyploidy would result in the formation of XXOO individuals for the heterogametic sex, and in the other case in XXYY individuals in the heterogametic sex In order to function normally the XXOO individual should produce XX and OO gametes and the XXYY individual should produce XX and YY gametes But there is no assurance that reduction will result in only XX and OO or XX and YY gametes. It seems probable that gametes of constitution XO or XY would also be formed. These, upon fertilization, would produce zygotes of constitution XXXO or XXXY. Such unbalanced chromosome constitutions tend to cause sterility or other abnormality and are selected against

The proof that such unbalanced chromosome constitutions lead to sterility and abnormality has been provided for Drosophila This, however,

[1] M. B Crane and W J. C. Lawrence, "The Genetics of Garden Plants," 4th ed., Macmillan & Company, Ltd., London, 1952.

is not true for all organisms Tetraploidy is known in the bisexual plant *Melandrium*, a member of the pink family Both XXYY and XXXY are normal males, a single Y chromosome being sufficient to determine maleness.

The only polyploid species of vertebrates in nature thus far reported seem to be among the fishes belonging to the salmon family, and the rodents. Sachs[1] has described what may be a case of tetraploidy in hamsters (Fig 106). He does not commit himself as to whether the golden

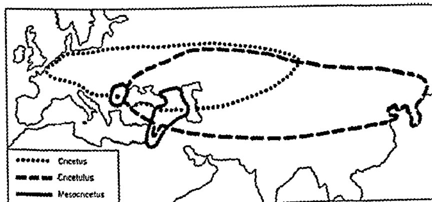


Figure 107. Geographical distribution of the hamsters *Cricetus*, *Cricetulus*, diploid; *Mesocricetus*, tetraploid (*From Sachs, Heredity*, 6 360, 1952)

hamster, which has double the chromosome number of two other species, arose from hybridization of two species or from the doubling of chromosome numbers within a species It is, however, interesting that the range of the supposed tetraploid species overlaps that of the two diploid species, which also overlap in distribution (Fig 107).

Additional evidence that the golden hamster is a polyploid is given by Sachs. (1) the other two species both have characteristically 8 mammae, while the golden hamster has 14 to 22, with no intermediates, (2) there is also paleontological evidence that the golden hamster arose more recently than the other two

SUMMARY

Let us now briefly summarize the leading theories of evolution As suggested by Wright,[2] these may be significantly grouped according to their inclusion or rejection of chance variation as a factor in evolution

[1] Leo Sachs, Polyploid Evolution and Mammalian Chromosomes, *Heredity*, 6:357-364, 1952

[2] Sewall Wright, The Material Basis of Evolution (review of book of this title by R Goldschmidt), *Sci Monthly*, 53:165-170, 1941; Population Structure in Evolution, *Proc Am. Phil Soc*, 93:471-478, 1949

Theories of Evolution Classified According to the Demands Which They Make on Chance Variation

I Chance variation not a factor
- *a* Inheritance of acquired characters (Lamarckism)
  1. Inheritance of effects of use and disuse, in animals
  2. Inheritance of direct effects of environment in plants
- *b* Orthogenesis (straight origin): an innate tendency to evolve in a particular direction irrespective of the environment, originally applied to evolution definitely directed by external circumstances

II Chance variation a factor (evolution a population problem)
- *a* Course determined by mass selection, operating on the net effects of random mutations
- *b* Course determined by interpopulation selection, operating by differential growth and dispersion of local populations differentiated by joint action of directed and random processes

This cleavage among the theories on the question of including chance as a factor coincides with the schism between the views of Western biologists and the official Soviet biology today. The presently dominant Michurin-Lysenko school in Russia rejects chance in biology. "By ridding our science of Mendelism-Morganism-Weismannism we will expel fortuities from biological science."[1] *Fortuity*, as defined in Webster's dictionary, is synonymous with *chance*. Obviously chance occurrences have their own efficient causal connections; hence there is nothing metaphysical about the concept of chance. While eliminating fortuities from their biology Lysenko and his followers have gone back to the discredited theories mentioned in group I above. Western biologists find no convincing evidence in support of these, they do find an abundance of evidence for the theories listed in group II.

CONCLUSION

No more concise summary of the parts played by the factors in evolution as discussed in the preceding pages has been discovered than the following statement by Wright:[2]

> I have attempted to form a judgment as to the conditions for evolution based on the statistical consequences of Mendelian heredity. The most general conclusion is that evolution depends on a certain balance among its factors. There must be gene mutation, but an excessive rate gives an array of freaks, not evolution; there must be selection, but too severe a process destroys the field of variability, and thus the basis for further advance; prevalence of local inbreeding within a

[1] Trofim Lysenko, "The Science of Biology Today," International Publishers Co., Inc., New York, 1948.

[2] Sewall Wright, The Roles of Mutation, Inbreeding, Crossbreeding, and Selection in Evolution, *Proc. 6th Intern. Congr. Genet.*, 1:356–366, 1932.

species has extremely important evolutionary consequences, but too close inbreeding leads merely to extinction. A certain amount of crossbreeding is favorable but not too much. In this dependence on balance the species is like a living organism. At all levels of organization life depends on the maintenance of a certain balance among its factors.

As an objection to evolution, the question is often asked, why have not all kinds of plants and animals evolved into complex higher species?



Figure 108. Sewall Wright, 1889– (*Courtesy of University of Chicago Magazine, photograph by Stephen Lewellyn.*)

The answer is that under evolution through natural selection no species is under the necessity of changing at all if it is already perfectly adapted —assuming that an organism can be perfectly adapted—to its environment. If the environment changes greatly, the species must of course change, migrate, or perish.

A second reason for the persistence of simple types is that simple species are adapted to occupy particular stations in the environment, or par-

ticular niches in the web of life, that more complex ones could never occupy. Speaking figuratively, a world with all kinds of environments calls for all kinds of inhabitants

Mutation is no doubt a universal phenomenon. As a consequence, nonadaptive changes have occurred and are still occurring in all species. Hence, no species is identical with its ancient ancestors The environment, also, changes repeatedly; this necessitates adaptive changes in those species that are to survive. If we can judge the future by the present and the past, it seems safe to predict that as long as our planet continues to be inhabitable, change will continue to be a universal law of life

What of the future of man? As a species, man is a newcomer on the earth He is less specialized than most of the mammals—if we except his special adaptations to the erect posture and his huge brain. It is his brain, above all, that has enabled man to become the most numerous, the most varied, and the most widely distributed of all the larger mammals Large numbers, great variability, wide distribution, and a generalized, rather than a narrowly specialized, body, all favor long life in a species Narrow specialization makes a species vulnerable during periods of rapid change in the environment.

In the past, extreme specialization in animals usually has preceded extinction—as is proved by the fossils in the rocks Does man's highly specialized brain imply the danger of his early extinction? For several reasons one may be justified in thinking that it does not In the first place, although the human brain is highly specialized with respect to its great size, it is generalized with respect to the uses to which it may be put Secondly, because of his highly developed brain man is able to modify to a very great extent his own environment—a thing that no other species is able to do But, most important of all, perhaps, man's highly developed brain enables him alone, among all living things, to look objectively at himself, to contemplate the process of evolution, and to control consciously and voluntarily the course of his own evolution. Within the limitations imposed by the world in which he lives and by his nature as he has inherited it from the past, man is therefore in a position to make of his future what he wills.

PROBLEMS

1. What was Mendel's position regarding the *fact* of evolution?
2. Distinguish between evolution and Darwinism
3. State the four biological laws upon which natural selection rests, with examples of each.
4. What is the standing of natural selection among biologists today?
5. Assume that a rare recessive sex-linked disease is found in 20 per 100,000 of

the males in the population If none of the affected persons reproduce, what rate of mutation is required in order to maintain the frequency mentioned?

6. Contrast Darwin's theory of the origin of the giraffe with Lamarck's theory

7 In what groups of organisms would you expect to find sexual selection? Name one in which it would not occur

8 Name the principal types of isolation Give examples of each

9. How does orthogenesis differ from other theories of evolution?

10 Account for the fact that tetraploid plants produced by hybridization are often fully fertile and true-breeding

11. Explain the fact that in thoroughbred race horses the color may be bay, brown, black, chestnut, roan, dun, or gray, with or without white spotting, while Hereford cattle are always red with white markings, and coach dogs are always white with black spots

12 Explain how the evolutionary progress of a species is favored by the alternate isolation of groups within the species, resulting in inbreeding, and the crossbreeding among the groups

13. How do you account for the fact that domesticated plants and animals—even those derived from a single species—are more variable than related wild species?

14 Account for the fact that the human species is much more variable than any wild species of large mammal

15 Does natural selection operate among modern civilized men? Illustrate your answer

16. What reasons can you give for regarding all human beings living today as members of one species?

17. What belief of Darwin's respecting the origin of hereditary changes is not generally accepted today in his country and in the United States? Why not?

18 What is a probable explanation of such cases as (1) the development of resistance to the antibiotic streptomycin by a strain of bacteria exposed to this chemical for a number of generations, (2) the appearance of a strain of houseflies or lice that is resistant to DDT in a region where this insecticide has been used for some time

19 A leading university in this country recently sent out an appeal for funds for medical research, in which the following facts were given "One hundred years ago, a man aged 60 had a life expectancy of 15 6 years today a 60-year-old man has a life expectancy of 15 5 years Why? In 1850, life expectancy at birth was only 38 3 years· today, it is 65 9 years " What answer to the above question "Why?" might a student of evolution logically offer? Use your general knowledge of the progress of medicine over the past century

20 Describe the sudden origin of a new species as a result of hybridization

15

HEREDITY IN MAN. I

Mendel's laws of heredity were discovered in plants, later confirmed in animals, and finally found to apply to man. The process of reproduction in man is very similar to that in other mammals (Fig 109) Mendel's belief in what he called the "unity in the developmental plan of organic life" has been proved correct beyond all doubt. A few examples of Mendelian characteristics in man illustrating a number of genetic principles have been given in previous chapters Research in human heredity is a very active field today. Books, monographs, and articles are appearing at an accelerating rate In spite of the difficulties inherent in the study of human heredity, we now have an extensive and ever-growing list of Mendelian characters, both normal and abnormal, in man From the evidence at hand it is clear that every system of the body, and perhaps every organ and structure, is subject to the influence of known genes. Tables 20 and 21 have been compiled from various sources to illustrate some of the most interesting and best-known Mendelian traits in man involving all the systems of the body. The tables include only a fraction of the known Mendelian human traits.

The age at which the characters make their appearance varies greatly. Some, such as polydactyly, develop long before birth; others, such as hair and eye color, may not develop fully until after birth. Some, for example juvenile amaurotic idiocy, appear in later childhood; while still others, illustrated by Huntington's chorea, usually develop in middle age.

The list shows that many relatively rare traits that are known to be Mendelian are injurious to the possessor. The general rule for organisms is that a change in a character through mutation is much more likely to be injurious than beneficial. The reason that mutations tend to be unadaptive seems rather obvious. According to present theories a gene is at least as complex an entity as a large protein molecule. Mendelian variations apparently result from sudden changes in the structure of the gene These changes, or mutations, are induced in some cases at least by forces outside the gene operating in a random manner. A random change in a physiological factor in the development of a complex organism should in theory most often produce an injurious effect, just as a random change

TABLE 20 MENDELIAN CHARACTERISTICS IN MAN*
(Arranged in the order in which they are considered in the text)

Dominant	Recessive	Page
SKIN, HAIR, NAILS, TEETH		
Piebald (skin and hair spotted with white)	Self color	309
White forelock	Self color	312
Dark hair (several genes)	Light hair	314
Nonred hair	Red hair	314
Freckles	No freckles	315
Pigmented skin, hair, eyes	Albino	316
Curly hair (hybrid, wavy)	Straight hair	316
Woolly hair (Caucasoid type)	Nonwoolly hair	316
Abundant body hair	Little body hair	318
Normal	Hairless (hypotrichosis)	319
Hairlessness (congenital hypotrichosis)	Normal	320
Early baldness (dominant in male)	Normal	190
Scaly skin (ichthyosis)	Normal	320
Thickened skin (tylosis palmaris et plantaris)	Normal	321
Absent teeth (various types)	Normal	323
Defective dentin (opalescent teeth)	Normal	323
Free ear lobes	Adherent ear lobes	324
EYES		
Brown	Blue or gray	326
Pigmented iris	Albino	326
"Mongolian fold" (uncertain)	No fold	329
Drooping eyelids (ptosis)	Normal	329
Normal	Nearsightedness (myopia)	329
Farsightedness (hyperopia)	Normal	330
Astigmatism (cornea not spherical)	Normal	330
Cataract (opaque lens)	Normal	330
Glaucoma (excessive pressure in eyeball)	Normal	331
SKELETON AND MUSCLES		
Dwarfism (chondrodystrophy)	Normal	333
Normal	Midget (ateliosis)	334
Extra digits (polydactyly)	Normal	335
Short digits (brachydactyly)	Normal	335
Split hand ("lobster claw")	Normal	336
Harelip and cleft palate	Normal	338
Rupture, susceptibility to	Normal	340
Absent long palmar muscle	Normal	342

* See Table 21, page 344, for other characteristics

in a complex nonliving machine is not likely to improve, but to reduce, the efficiency of the machine. Only rarely should a mutation result in an adaptive change or even in a change that is neutral in effect

Another explanation for the failure of lists such as Table 20 to show many pairs of normal alternative traits is that such traits are likely to

be complex Characters that show continuous variation, such as stature and skin color, are affected by many interacting genes The usual pedigree studies do not reveal segregation and assortment among these.



Figure 109. Human egg at moment of fertilization Numerous sperms in contact with the egg, several penetrating its outer layers, one polar body. Compare with photograph of mouse egg, Fig 24. (*Courtesy of Dr. Landrum B. Shettles.*)

A glance at the list shows us that mutations from the normal may be either dominant or recessive or that there may be no dominance. In man, recessive mutations probably are more numerous than dominant ones, just as in the lower mammals, in spite of the fact that tabulated lists often suggest the opposite. No doubt most persons carry many recessive genes in the heterozygous condition without knowing it, because the usual

mating is between unrelated persons who are not likely to carry the same recessive; the character therefore cannot develop In pedigrees of dominant traits, the characteristic under investigation shows up in each generation (provided it is due to a single gene with complete penetrance), while a recessive frequently skips one or more generations For this reason it is much easier to find pedigrees showing dominant mutations than pedigrees of recessive mutations.

It is probable that many of the traits listed as dominants would be found to illustrate incomplete dominance if we had all the facts With many of the rare pathological traits there is no evidence that a homozygote has been observed. Defectives do not ordinarily marry defectives In a few cases where such matings have occurred, an extreme defective, probably a homozygote, has been produced

Let us now consider in some detail the individual traits listed in the tables in connection with sample pedigrees of some of them

SKIN, HAIR, NAILS, TEETH

The most comprehensive work that has appeared in English on the heredity of the skin, hair, nails, and teeth is a book by an English physician, Cockayne.[1] This valuable work of nearly 400 pages is a mine of information for those who care to delve further in this field. One might gather from reading Cockayne that the skin and its derivatives are peculiarly susceptible to gene mutations, especially injurious ones, since more than 100 separate hereditary defects are listed But while this may be so, it is also true that skin structures, lying on the outer surface of the body as they do, are more readily noticed and more easily studied than most others. Parenthetically, it may be remarked that the physician is in an unusually fortunate position to observe inherited abnormalities of all kinds. When there arises a generation of physicians, all of whom have had some training in genetics, we may expect a rapid increase in our knowledge of human heredity A trend in this direction has been noticeable in the past few years, as medical schools more and more come to offer their students basic instruction in human genetics

White Spotting (Piebald)

In Chap 6 we discussed the heredity of skin color in crosses between the Negro and white races The genes there considered affect the development of pigment more or less uniformly over the body But other genes are known which affect the distribution of pigment in localized areas, resulting in a white-and-dark-spotted (piebald) pattern. Piebalds have been

[1] E. A Cockayne, "Inherited Abnormalities of the Skin and Its Appendages," Oxford University Press, London, 1933

found in all three major divisions of mankind (Caucasoid, Mongoloid, and Negroid) in various countries of the world since early times. There are several different types of spotting in man, due apparently to distinct mutations Their counterpart is found in many domesticated mammals in which a variety of types of dark and white spottings occur. In dogs, for example, there is a dominant type of white spotting known as harlequin (Chap. 19), in which many small black spots are scattered more or less uniformly over a white ground, as illustrated in the Great Dane and



Figure 110. Children of the fourth generation of white spotting (piebald), inherited as a simple dominant (*From Sundför, J. Heredity.*)

the Dalmatian coach dog There is also a recessive white spotting in dogs, illustrated in the bull terrier and collie, in which there are a few large spots of white, chiefly on the head and underparts.

In man the most frequent type of white spotting that regularly involves large areas of the skin is a dominant. Hans Sundför of Norway has published a complete description of a Norwegian family in which this type of white spotting, known as piebald, has been traced through four generations.[1] His description is accompanied by excellent photographs and drawings The pattern tends to follow the same general lines in all cases, although the size and area of the white spots are quite variable, as in many other mammals.

There is a "blaze" of white in the frontal region centering at the hairline and frequently extending down the forehead (Fig. 110). In some individuals the blaze is very small; in others, it extends back to the crown. A large unpigmented area, irregular in outline, occurs on the chest and

[1] Hans Sundför, A Pedigree of Skin-spotting in Man, *J. Heredity*, 30:66–77, 1939.

abdomen, and unpigmented spots are found on the arms, especially on the elbow side (Fig. 111).

The legs show large unpigmented spots centering at the knee and usually extending about halfway down the lower leg and up the thigh and sometimes joining the white spot on the abdomen

The back, hands, feet, shoulders, back of neck, and head (excepting the blaze) are usually normally pigmented The spots are hardly noticeable in fair-skinned persons when the skin is kept covered, but stand out



Figure 111. Girl of the fourth generation of white spotting (piebald). Similar unpigmented spots are on the forehead, legs, chest, and abdomen of this girl *(From Sundför, J Heredity)*

sharply upon exposure to the sun because of the tanning of the pigmented regions Unpigmented regions do not tan

According to Cockayne, who has tabulated the early pedigree studies of families with this type of white spotting, one of the parents of white-spotted children is always white-spotted, there being no case on record of two normal parents producing a spotted child The same thing was reported by Sundför, who also reports that no marriage between two affected persons has taken place in the family he studied

The ratio among all the children tabulated by Cockayne is 133 spotted: 118 nonspotted. In the Norwegian pedigree it is 40 spotted·20 normal, with 5 doubtful Adding all together, the ratio is 173 spotted:138 nonspotted (five doubtful). This makes a considerable excess of spotted individuals, since the expected ratio from a backcross mating is 1:1. This

deviation from expectancy, however, may be due merely to chance, since by an application of the chi-square test, described in Chap. 3, it can be shown that in accordance with the law of probability one time in 20 we would expect as great a deviation from equality in flipping a coin 311 times There may of course be some other explanation, such as a failure to record all of the normal individuals.

White Forelock

A type of dominant white spotting that is frequently observed and for which several pedigrees have been published is known as white forelock,



Figure 112. Mother and sons representing the fourth and fifth generations, respectively, of white forelock. The older boy does not have a white forelock, but there is a white spot on one leg (*From Fitch, J. Heredity.*)

since it is ordinarily limited to a white spot on the mid-line at the junction of the scalp and forehead (Fig. 112).

When the hair is combed back, as is the mother's in the picture, there

is a false impression of a stripe In position and appearance the spot is similar to the piebald spotting previously described, but it is usually smaller. Although the relation of white forelock to piebald is somewhat uncertain, the two have always been considered as separate mutations In a pedigree published by Fitch[1] (Fig 113) the inheritance of white forelock is shown through five generations, the last two of which are represented in the photograph (Fig 112)

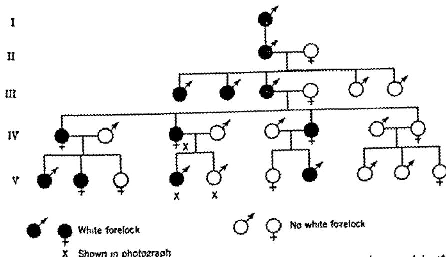


Figure 113 Pedigree showing inheritance of white forelock as a dominant trait through five generations. (*From Fitch, J Heredity*)

In this family, according to Fitch, the white forelock is often accompanied by a few white spots in the skin on various parts of the body The boy without the white forelock, in the photograph, has a white spot on one leg; he is the only member of the family known to be so marked It seems not unlikely that white spots might be found in the skin of most affected individuals if they were looked for carefully, and that this condition differs from piebald spotting only in degree

Hair Color

The study of hair color in man is complicated by the fact that the hair contains two pigments· (1) a granular melanin, which varies in intensity from black through various shades of sepia to "ash blond," or from dark brown to light golden blond; and (2) a diffuse pigment, which varies from dark red to yellow Hair color is, therefore, really a resultant of two characteristics· intensity of pigment and quality of pigment The situation is similar in other mammals Although the chemistry of these two pigments

[1] Lyle Fitch, Inheritance of a White Forelock, *J. Heredity*, **28**:413–414, 1937

is imperfectly known, it is certain that there are genes which affect either one pigment or the other alone, and other genes which affect both pigments; some genes primarily affect intensity of pigment, others primarily affect quality of pigment.

In the case of guinea pigs, in which the heredity of hair color has been analyzed more thoroughly perhaps than in any other mammal, we have seen (Chap 6) something of the complexity of the character. The effects of some of the principal genes involved have been studied exhaustively by Wright. Many years of laborious experimentation involving many generations of animals, under practically ideal conditions, were necessary for the solution of the problem in guinea pigs Therefore it is not surprising that in man there are still some uncertainties Here the situation is probably as complex as in guinea pigs, but in man investigation is limited to chance matings, with only a few generations available for study. Discoveries of biological laws in the lower animals offer valuable clues to the conditions in man, but since details of heredity usually differ from species to species, the rules for each must be worked out separately.

In man, with respect to intensity, dark hair dominates more or less over light hair, and with respect to quality, black or brown dominates over red In marriages between persons with intense black hair (Eskimos) and light blonds (some Scandinavians), the children, according to the noted anthropologist and explorer Stefansson[1] and other observers, are essentially black-haired. The results are not so clear in marriages between blonds and brunettes among whites, here the children are often intermediate, with varying shades of hair color. Such results, however, do not necessarily show a lack of dominance, because in a population made up of both blonds and brunettes, the brunette may not be purebred If there is a series of alternative genes (multiple alleles) affecting the intensity of pigmentation, as in the guinea pig, a brunette might be heterozygous with respect to any one of them. The fact that there are so many different shades of sepia and brown hair in man is evidence that there are several genes affecting melanin pigment. Dominance is probably incomplete among some of them In marriages between two light blonds, on the other hand, it can be safely predicted that the children will be blonds rather than brunettes. A further complicating factor is the darkening of the hair in many blonds during growth from childhood to maturity.

Red hair in many pedigrees seems clearly to be due to a single recessive gene. With few reported exceptions, in marriages between red-haired persons the children are all red-haired—as they should be if red is recessive. Moreover, red-haired children are frequently born to parents who do not have red hair, and the 3:1 ratio of nonred to red is what would be

[1] Vilhjalmur Stefansson, "The Friendly Arctic," The Macmillan Company, New York, 1921.

expected if red is a single recessive Cockayne quotes studies of a group of families in which only one parent had red hair and at least one red-haired child was born; the ratio was 46 red 48 nonred, which is almost a perfect 1:1 ratio, as expected from a backcross mating between a hybrid and a recessive

One difficulty in the study of red hair in man is that of classification. There are various types of "red," indicating several different genes Some of these so-called reds are not recessive If there is a type of red hair in man that is due to a recessive gene, as seems unquestionable, it agrees with what is known in guinea pigs, cattle, horses, hogs, and other mammals.

Skin Color

There is considerable correlation with respect to the color of the skin, hair, and eyes in man Dark-skinned individuals, as well as dark-skinned races, tend to have dark hair and dark eyes, while light-skinned individuals, as well as races, tend to have light hair and light eyes The correlation between skin color and hair color is not surprising, since the hair is an outgrowth of the layer of the skin which contains the pigment, namely, the epidermis. The iris of the eye which contains the pigment giving the characteristic color to the eye is indirectly related to the epidermis in that both are derived from the outer embryonic layer known as the ectoderm.

The three major divisions of mankind (Negroids, Mongoloids, and Caucasoids) are distinguished to a certain extent by skin color, though by itself this is of little value as a racial distinction because of the great variability in color in all three groups and the overlapping of one group by another. The lighter shades of color among whites of European origin have probably arisen through successive mutations from darker types

The existence of genes affecting the color of hair, eyes, and skin independently explains such combinations as black hair, blue eyes, and fair skin in individuals of some Irish families, black hair and fair skin in some Jews; and yellow hair, brown eyes, and light skin among various other Caucasoids.

Many interesting combinations can be observed among mulattoes The writer saw two young male mulatto students, both with approximately the same shade of yellowish-brown skin, one having black hair and light-hazel eyes, the other having light-brown hair and dark-brown eyes

Red-haired persons usually have very little pigment in the skin, and what pigment there is tends to collect in patches (freckles) Freckles, however, are not limited to red-haired persons Cockayne reviews a number of studies on the heredity of freckles and concludes that freckles are the result of a single dominant gene.

The true albino, in which pigment is almost entirely lacking in skin, hair, and eyes, has been considered in Chap 2 Albinism is a single recessive mutation found in all races The hereditary basis of the differences in skin color between Negroes and whites was discussed in Chap 6

Woolly Hair

The inheritance of the usual types of straight, wavy, and curly hair of Caucasoids has already been discussed in Chap 2 The typical hair of Negroids, variously known as woolly, kinky, or frizzy, is quite different, both genetically and structurally, from curly hair Woolly hair grows in the form of a spiral within the follicle. In cross section the individual hairs are on the average more flattened than in straight hair, although there is considerable variability in the hairs of the same head, and even in different regions of the same hair [1]



Figure 114 Woolly hair in a Caucasian woman, inherited as a simple dominant mutation (*From Mohr, J Heredity.*)

In crosses between whites and full-blooded American Negroes originating in West Africa, the woolly hair seems to depend upon several genes. In mixed marriages producing children of various percentages of white and Negro blood there is considerable variability in hair form, ranging from woolly through closely curly, very wavy, to slightly wavy. More extensive studies of pedigrees involving Negro-white crosses are necessary before the method of inheritance can be determined.

Woolly hair in white families has been reported in three isolated instances, following several earlier reports The first of the three is by Professor Otto L Mohr, The University, Oslo, Norway.[2] He has written a complete description of the characteristic, illustrated by excellent photographs—one of which is reproduced (Fig 114)—and a pedigree covering five generations From his personal investigations he concludes that the hair in its main features is like the hair of the woolly-haired races, but that it must have occurred in a European stock as the result of an independent dominant mutation

Mohr believes that any intermixture of Negro blood in this family may be safely excluded, since the family is of Norwegian farmer descent known for seven generations showing the clear "Nordic" type. He says,

[1] Madeline Kneberg, Improved Technique for Hair Examination, *Am. J. Phys Anthropol*, April–June, 1935

[2] Otto L. Mohr, Woolly Hair a Dominant Mutant Character in Man, *J. Heredity*, **23**:344–353, 1932.

Even nowadays, with the highly developed means of communication, a negro is practically never seen in Norway And the occurrence of a negro × white cross or a hybrid × white crossing of this order more than seven generations back is for social and other reasons so improbable that it may safely be left out of account.

He thinks the origin of the character from a Negro cross is ruled out also by the fact that in Negroes woolly hair is not due to a single dominant gene

Mohr describes the hair as being very strikingly curled or frizzled, similar to Negro hair. The curling is of a spiral type As in the Negroids, the hair never reaches a great length—in the family under discussion not more than about 14 cm Although it continues to grow, it normally breaks off while still quite short In cross section the hair of the woolly-haired individuals is, he writes, "characterized by a flattened shape, giving the cross-sections a flattened oval, or in some cases—presumably near a twist—a kidney-shaped form " The hair is usually very light-colored in childhood and gradually turns darker with age, in some cases, however, a woolly-haired individual had dark hair

The ratio of woolly hair to normal hair among the children from all 20 matings of woolly hair × normal hair as shown in the pedigree is 38 woolly-haired 43 normal-haired, in 3 the hair type is unknown This is a very good 1.1 ratio, as expected from a backcross of hybrid to recessive

The second case of woolly hair in Caucasoids is described by Dr C Ph Schokking, of the Royal University of Leiden, Holland [1] The author comes to exactly the same conclusion regarding its heredity as Mohr does In a village near Leiden, Schokking found a number of woolly-haired persons belonging to the same Dutch "peasant" family The pedigree shows the trait in five generations without the skipping of a generation There is a total of 13 woolly-haired.17 normal-haired individuals from marriages of woolly × normal The published photographs show most of the individuals, both woolly-haired and normal, with quite dark hair; otherwise, the hair appears much like that in the Norwegian family. Schokking found no correlation whatever between form of hair and color of hair The description of the structure of the woolly hair, including its brittleness and flattening, agrees perfectly with Mohr's description The author states, "In no one of the members of the family was the slightest trace of any other character of a colored race to be found "

Schokking summarizes the data from the families reported by himself and Mohr, together with that from three earlier workers. The resulting combined ratio is 138 woolly: 125 normal, which is a very good 1:1 ratio.

[1] C Ph. Schokking, Another Woolly-hair Mutation in Man, *J. Heredity*, 25:336–340, 1934.

The last reported case of woolly hair, which agrees entirely with those already cited, was discovered in the southern United States by Edgar Anderson [1] The published pedigree shows the characteristic appearing in five generations, in a ratio of 1 1. The family came from "Old American stock" The author states,

To one accustomed to the woolly hair of negroes and many mulattoes, the peculiar hair exhibited by these pedigrees seems something quite different It has an open, unmatted appearance and gives the impression of a peculiar kind of hair rather than of negro hair As a matter of fact, I first saw the young woman who supplied the information from a passing automobile, but even at that distance recognized the condition as being similar, if not identical, with that illustrated in *The Journal of Heredity*

This raises an interesting question as to whether the woolly hair in the three families mentioned arose from three independent mutations. Mohr states that quite a few members of the Norwegian family migrated to the United States where their descendants now live Could the American family described by Anderson trace back to these? Norway and Holland are near enough to one another that a common origin of the mutation seems not impossible

Hair on Body, Face, and Limbs

Man is peculiar among all mammals in the distribution of hair over the body, having normally a heavy growth of hair on the scalp, axillae, pubes, eyebrows, and—in the male of some races—on the face, accompanied by a very scanty growth on other parts of the body. Some other mammals, however, especially some of the Primates, show tendencies in the same direction The growth of hair in man is more variable than one might realize in view of the habit of covering the body with clothing, and of shaving and cutting the hair.

The growth of hair on the body and face in man varies among the races as well as among individuals within a race, and also between the sexes The hairiest people are the Ainus (probably of primitive Caucasoid stock) who inhabit the northern part of Japan. Whites come next, then Negroes, with the Mongoloids, including Eskimos and American Indians, least hairy of all. In the Mongoloids, especially the American Indians and the Eskimos, the lack of body hair is pronounced; even the beard is very scanty. These racial differences are of course hereditary, but just how many genes are involved is not known.

In white people, relative hairlessness of the body and limbs seems to be recessive, while excessive hairiness is dominant, although pedigree

[1] Edgar Anderson, An American Pedigree for Woolly Hair, *J. Heredity*, 27:444, 1936.

studies are inadequate. This type of relative hairlessness found normally in man is quite different from those which occur as mutations in the domesticated mammals. In the latter the scalp as well as other parts of the body are devoid of hair and therefore have more resemblance to the congenital types of baldness in man.

In man, the male has more body hair than the female, among genetically similar individuals. This is probably due to the influence of the male sex hormone which is known to be the direct cause of growth of the beard in the male. The occurrence of superfluous hair on the face in women was studied by Trotter and Danforth, who came to the conclusion from the high correlation (about 0.8) between mothers and their daughters that it probably was due to a dominant gene, although this could not be proved by the usual pedigree method, since the gene effect in the male is obscured by the beard.[1] Among about 1,700 women examined, slightly over 27 per cent showed superfluous facial hair. The percentage was the same for colored women as for white women, and the same for normal women as for those in mental hospitals. The authors found no evidence of selection against facial hair in women.

Hairlessness (Hypotrichosis)

There are several distinct types of hairlessness in man. Its study is complicated by the fact that infections are a factor in some types. An extensive review of reported cases in which heredity plays a major role is given by Cockayne. In one type of extreme hairlessness, inherited as a recessive, the scalp is either entirely bald or almost entirely so from birth, or soon after birth. There is a strong tendency also for hair to be missing or scanty on other parts of the body. Eyebrows and lashes, for example, are commonly missing or very thin, while in some families the nails, and rarely the teeth, are imperfectly developed. The variations with respect to the expression of the trait makes it likely that several independent mutations have occurred.

This type of hairlessness agrees in general with many cases of recessive hairlessness found in domesticated mammals. Recessive hairlessness, more or less complete, has been found in horses, cattle, sheep, goats,[2] hogs, rabbits, rats, mice, and cats.[3] The genetic cause of the normal hairlessness of certain wild animals (walrus, whale, hippopotamus, rhinoceros, and elephant) is not known, but the condition is probably the result of mutations from hairy ancestors. In recent prehistoric times hairy ele-

[1] M. Trotter and C. H. Danforth, The Incidence and Heredity of Facial Hypertrichosis in White Women, *Am. J. Phys. Anthropol.*, 5:391–397, 1922.

[2] D. Kislovsky, Inherited Hairlessness in the Goat (with Literature Cited), *J. Heredity*, 28:264–267, 1937.

[3] Etienne Letard, Hairless Siamese Cats, *J. Heredity*, 29:173–175, 1938.

phants and rhinos lived in Europe and were hunted by primitive man—as we know from the discovery of their actual remains as well as drawings of them made by cave man The lack of hair in the wild species mentioned is, in some cases at least, an adaptation to aquatic or to tropical habitats.

Dominant extreme hairlessness has been reported in many different human families, including a tribe of Australian blacks. As a rule the body is otherwise normal. Dominant hairlessness is found in dogs, of which the Chihauhuan hairless breed of Mexico is the best-known example Also, a dominant type of hairlessness has been found in mice.

Scaly Skin (Ichthyosis Vulgaris)

The skin in man is a complex organ which develops from two distinct layers of cells, the inner layer, or dermis, and the outer layer, or epidermis It contains a rich supply of blood vessels and nerve endings and is closely set with two types of glands (sweat glands and sebaceous glands) and, except in a few regions, with numerous hair follicles Unlike most organs, the skin does not cease growing in the adult, but continues to produce new cells in the deeper portion of the epidermis while the cells near the surface become flattened, hardened, and dried. An imperceptible shedding of these outer dead cells goes on more or less constantly.

The foregoing facts are mentioned as a necessary background to the appreciation of the many hereditary abnormalities in the structure of the skin The large number of such abnormalities dependent upon separate genes proves that normal development of the skin depends upon the cooperation of many genes. This is what we should expect in an organ as complex as the skin

Most of the defects of development of the epidermal layer are grouped under the heads of ichthyosis, tylosis, and related conditions. Cockayne has assembled the literature, classified the cases, and written an account of them covering sixty pages. Two of the most common types are considered below.

Ichthyosis, in its most common form (ichthyosis vulgaris), is described by Cockayne as follows.

> The skin is dry and covered with small scales, which are continually being shed in the form of a fine branny desquamation. The face is usually a little glazed in appearance, but otherwise normal, and the skin of the flexures, perinaeum, and genital region is little altered in texture. On the knees and elbows the cornification reaches its maximum, and on the extensor surface of the limbs it is greater than on the flexor surface. The scalp is scaly and the hair thin and dry; the eyebrows are scanty and their outer third may be almost absent, and on the trunk and limbs the hair is sparse and atrophic. The nails are dry and brittle. The palms and soles are dry and smooth with the finer lines obliterated and the deeper ones

accentuated. The secretion of sweat and sebum is deficient on the most ichthyotic parts, but on the palms and soles and in the flexures sweating may be normal.

The condition first becomes recognizable in the early months of infancy and gets gradually more noticeable, until at about 10 years of age it is fully developed and thenceforward remains unchanged through life The physique is fairly good and the general health is unimpaired, but the ichthyotic skin is very liable to mild inflammation.

Histologically the most conspicuous abnormality is a thickening of the horny layer of the epidermis, the cells of which are unduly adherent . .

Ichthyosis vulgaris is one of the most frequently inherited defects of the skin, but Cockayne finds that few pedigrees have been published Some of the pedigrees indicate a single dominant, others show the skipping of a generation, and hence require some other explanation. In one group of pedigrees the inheritance is that of a sex-linked recessive

Thickened Skin (Tylosis palmaris et plantaris)

Tylosis (Gr., a making callous) refers to a thickening of the skin, particularly of the epidermis In the well-known hereditary type, named above, the abnormality is restricted to the palms and soles A very clear description of this defect has been given in a recent study of a family from Belfast, Ireland,[1] from which the following is abstracted

A total of 19 affected persons were seen in this family, and the authors consider the evidence good that 22 others who are dead or who could not be seen were also affected

The condition was detectable in a minority of cases at birth, and in all within a few weeks. The first sign in infants is a branny scaling off of the palms When the defect is fully developed the skin on the palms of the hands and soles of the feet is thick and horny and the normal flexure lines become deep cracks The thickened skin extends from the tips of the fingers to the fold of the wrist On the soles of the feet the skin that comes in contact with the ground is thickened in the same manner as that of the palms

After much sweating the palms and soles become tender, and infections sometimes develop in the cracks These symptoms become more pronounced following manual labor.

There is in most cases periodic peeling of the hard skin, and the harder the skin the larger the pieces that are shed The frequency of peeling varies from about once a year to two or three times a year

Accounts were given of two or three members of this family who had tried various remedies. All agreed that the thickening could be rubbed down with "sandstone" or pumice, to give a better cosmetic effect and

[1] A C Stevenson and D N. F Scott Pearson, The Inheritance of Tylosis Palmaris et Plantaris in a Large Family, *Ann Eugenics*, 18:9–12, 1953.

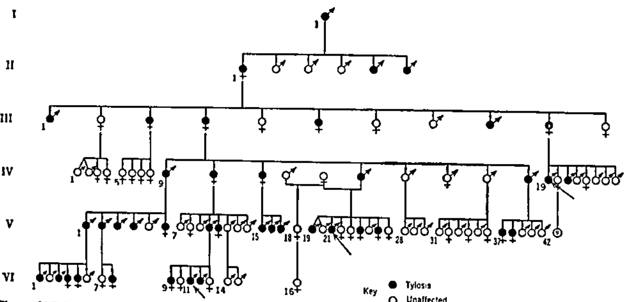


Figure 115. Pedigree of tylosis palmaris et plantaris in a large family, showing the trait transmitted through six generations as a typical dominant. (*From Stevenson and Scott Pearson, Ann Eugenics*, 18:11, 1953.)

at times relief from discomfort One had had "X-ray treatment" without effect, and one man while serving in the Royal Navy had had some kind of exfoliative treatment which left him with normal-looking hands. They were, however, so painful that he was discharged from the service and within a few months the condition was as before

The pedigree, reproduced in Fig 115, is that of a typical dominant There is no skipping of a generation The ratio of affected to normal among the offspring of affected parents (40 affected 41 normal) is as near to a perfect 1:1 as possible Males and females are affected alike Every affected child had an affected parent There are no cases of the marriage of two affected individuals, and the authors state that they can find none in the literature We therefore do not know what a double dose of the gene might produce There is in this pedigree no evident tendency of affected parents to limit the size of their families

Absent Teeth

Embryologically the teeth have a common origin with the skin, and a number of genes are known which simultaneously modify the development of both Among genes which seem to affect only the teeth are those for the following· absence of one or more of the premolars (dominant), absence of upper incisors and molars (dominant), absence of the two central incisors above and below (mode of inheritance uncertain), and absent or reduced upper lateral incisors (dominant—one of the most common abnormalities of the teeth) As in other Primates, the upper lateral incisors are normally much smaller than the central incisors As pointed out by Darwin, structures that show reduction in size are often highly variable or absent.

Defective Dentin

Hodge and Finn[1] have compiled pedigrees of three unrelated families showing a distinct type of gross defect of the teeth known as "opalescent dentin" inherited as a dominant In cooperation with numerous colleagues they made elaborate clinical studies of the affected persons, together with microscopical, chemical, and physical studies of the teeth Their report is commendable for its clarity and completeness

The authors state that the defect is characterized clinically by extreme translucency, discoloration, friability, and wearing away of the teeth The dentin is extremely soft, the enamel has a gray or bluish color, although appearing normal microscopically. There is little tooth decay, although mass destruction of the crowns and their early excessive wear often simulate rampant caries The crowns are originally of average size,

[1] H C. Hodge and S. B. Finn, Hereditary Opalescent Dentin, *J. Heredity*, 29:359–364, 1938

but the roots are short Pulp chambers are absent, and pulp canals are completely or partially obliterated.

The clinical studies of affected persons were negative in that they showed no peculiarity of physiological reactions not present in normal members of the families.

One of the families was of recent Italian descent, one was of German-Irish descent, and the third was of American stock living as missionaries in China and India. The pedigree of the American family is shown in

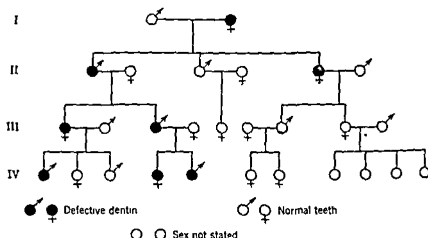


Figure 116. Pedigree showing the inheritance of defective dentin (opalescent teeth) Defective dentin is dominant. (*From Hodge and Finn, J. Heredity.*)

Fig 116; it is quite typical of a single dominant The other two pedigrees are consistent with the one given. Evidently the trait is not extremely rare as judged by the numerous reports cited by Hodge and Finn.

Ear Lobes

Whether the ear lobes shall hang free or grow attached seems to depend upon a single gene The form of the ear lobe (Fig. 117) is a good example of a difference having no adaptive value. It is purely a matter of taste as to which type of ear lobe one may prefer. An observer in this country will soon be convinced that attached lobes of the type shown in Fig 117 are in a small minority. No statistics on the frequency of attached lobes seem to have been published.

A number of pedigrees have been published indicating that free lobes are dominant and attached lobes recessive. One of these showing clear-cut segregation (Fig. 118) was reported by Powell and Whitney.[1]

[1] E. F. Powell and D. D. Whitney, Ear Lobe Inheritance, *J. Heredity*, 28:181–186, 1937.

Although in some families there seems to be a sharp segregation of free lobes and attached lobes, this apparently is not true in all families Dr. A S Wiener[1] reported studies of 124 families and 607 children in which all gradations between attached and free ear lobes occur He states that



Figure 117. Two distinct types of ear lobes in man. *Left* Free lobes *Right* Adherent lobes In many pedigrees free lobes are dominant

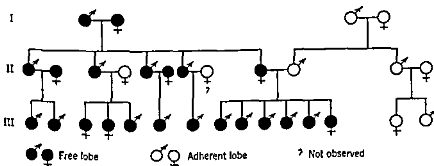


Figure 118. Pedigree showing two types of ear lobes Free lobes probably dominant (*From Powell and Whitney, J. Heredity*)

rarely in the same individual one ear lobe may be free and the other attached He has classified the individuals studied into four arbitrary groups· completely free ear lobes, completely attached ear lobes, and two intermediate types. The data are presented in tabular form without individual pedigrees and without photographs.

Wiener concludes that although there is a definite correlation between the types of ear lobes in the parents and children, more than a single gene probably is involved. This is to be expected. Clarification of definitions is needed: the type illustrated on the right in Fig. 117 might better be

[1] A S Wiener, Complications in Ear Genetics, *J Heredity*, **28**:425–426, 1937.

termed *lobeless* Further studies of this trait should yield interesting results

EYES

One of the most comprehensive works ever published on the heredity of eye characters in man is a book by Dr P J Waardenburg,[1] eye specialist of Arnheim, Holland In his excellent volume of more than 600 pages, including 197 figures and eight colored plates, there are descriptions of well over 100 hereditary eye variations (largely defects) in man The literature list is unusually extensive The book should be consulted by anyone who has a special problem in this field Unfortunately it has not been translated into English from the German in which it is written

The eye is one of the most complex organs in the body. The eyeball itself is made up of several complex layers, while inside the eyeball are the iris, lens, vitreous body, and muscles for changing the curvature of the lens. Attached to the outside of the eyeball are six muscles which move the eye in all directions Finally, there are the lids, with the associated lachrymal (tear) glands and Meibomian (oil) glands. In order that the eye may develop into a perfect optical instrument there must be coördinated development of all of these parts No wonder that so few persons have really perfect eyes and that gross developmental defects are not uncommon. The list of eye defects is an imposing one, and it is still growing.

There are a few well-known hereditary eye differences which are recognized as racial differences and are not to be regarded as abnormalities These include color of the iris and form of the upper eyelid.

Eye Color

Ordinary eye colors are due to the presence of pigment in the cells of the iris According to Waardenburg, in all shades of eyes from dark brown to blue there is a double layer of cells containing granules of a dark-brown pigment covering the back of the iris There are in addition, in all eye colors except blue and gray, branched pigment cells containing a lighter-colored yellow or brown pigment scattered in the connective tissue of the iris The differences in eye color depend largely upon the number, the color, and the arrangement of these branched cells If the branched pigment cells are absent or very few in number, the dark-brown pigment on the back of the iris shines through the body of the iris, making it appear blue or gray. Increasing numbers of branched pigment cells account for green, hazel, and brown eyes. In complete albinism, pigment is practically absent from both the back and front layers of the iris, and light reflected from the blood in the vessels of the iris gives it a red or pink color.

[1] P. J. Waardenburg, "Das menschliche Auge und seine Erbanlagen," Martinus Nijhoff, The Hague, 1932

As we have seen (Chap 2) albinism is due to a single recessive mutation. If the gene for albinism is present in a double dose, the eye and the skin and hair as well are practically free of pigment, regardless of what other genes are present. This is shown by the reported fact that the children of an albino Negro mated to a blond white are typical mulatto children; the Negro albino has all the genes for pigmentation except the dominant alternative of albino, and this is supplied by the blond white

Anthropologists have called attention to the fact that the great majority of mankind have dark-brown eyes. This includes all the Negroid division except rare mutants, nearly all the Mongoloids except a tribe of Eskimos in northern Canada (possibly an ancient mixture of Eskimos and Scandinavians), and a few Indians in Central America, and a majority of Caucasoids (including the East Indians) Among the Caucasoids, blue eyes are practically limited chiefly to some of the Berbers (a mixed group living in northern Africa) and to the Nordics and East Baltic peoples of northern Europe, and to their descendants.

Owing to the relatively small numbers of light-complexioned people as well as to their limited geographic range, it is supposed that the original eye color in man was dark brown and that the lighter colors are relatively recent mutations This view is supported by the fact that most other mammals in a state of nature have dark eyes.

Several investigators attempted to solve the problem of the inheritance of eye color in man before Mendel's work became known in 1900, and many haue worked on it since that time Although the problem still offers some puzzles, it is now generally recognized that there must be more than one pair of genes involved, for with only one pair of genes, even assuming lack of dominance, there should be only three eye colors instead of the six or more principal types that actually exist

Waardenburg,[1] after reviewing the work of other investigators in connection with his own studies, comes to the following definite conclusions regarding the inheritance of eye color in man·

1. Two blue- or gray-eyed parents have only blue- or gray-eyed children; blue or gray is recessive, and brown is dominant. Green eyes, unlike blue and gray eyes, show yellow or brown spots, their genetic basis is different.

2. There are independent genes which are responsible for the various other colors mentioned Some of these genes affect the amount of pigment; some, its localization (in the form of scattered spots, rings around the pupil, etc); and others, its quality (light yellow or dark brown).

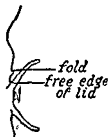
3. In general, the darker eyes are dominant over the lighter, as green over blue

4 Much work remains to be done before a complete explanation of the genetics of eye color in man can be given.

[1] Ibid



Complete Mongoloid

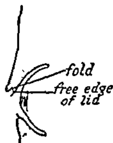




No Fold



Internal Epicanthus





External Epicanthus



Median Fold

Figure 119. Human eye folds. In each case the right eye is represented (*From Hooton, "Up from the Ape," The Macmillan Company.*)

Eyelids

Anyone who has observed Mongolians (Chinese, Japanese, etc) must have noted a peculiarity in the appearance of the eye—the "slant eye," "slit eye," etc., of various writers As a matter of fact, the eyeball itself is not different from that in other races, nor is its position in the skull essentially different. The distinctive appearance is due primarily to an extra fold of skin (the "*Mongolian fold*"), which extends from the upper lid down and over the inner corner of the eye toward the nose, making a new angle with the lower lid (Fig. 119). If this fold is lifted up, the shape and position of the eye and lids are seen to be essentially the same as in other races. The Mongolian fold occurs in a small percentage of persons of European descent, owing probably to early racial mixing It is found in the great majority of Mongolians, though not in all There is no doubt that it is an inherited trait. The few studies made of its genetics in racial crosses suggest that the Mongolian fold may depend upon a single dominant gene

A defect of the upper lid that is not to be confused with the Mongolian fold is known as *ptosis*, or drooping eyelids The muscles which raise the upper lids are unable to function, so that only a narrow slit is possible between the two lids In a pedigree of six generations worked out in this country by Briggs,[1] the defect was shown to be dominant Several types of ptosis are described by Waardenburg, in which other defects of the eyes accompany the ptosis In some of the types the whole complex is inherited as a recessive.

Nearsightedness (Myopia)

In nearsighted eyes the rays of light coming from a distance are brought to a focus in front of the retina rather than on the retina as in normal eyes. This causes the image of distant objects to be blurred. Without glasses a nearsighted person cannot see clearly unless the object is very near. Anatomically there seem to be at least four factors that may play parts in the causation of myopia: (1) length of eyeball, (2) refractive power of the cornea, (3) depth of the anterior chamber, (4) refractive power of the lens. In many cases myopia may be due to a combination of factors producing excessive refraction.[2] A frequent accompaniment of extreme nearsightedness is an abnormally long eyeball

Nearsightedness is a very common defect, estimated by some as affect-

[1] H H Briggs, Hereditary Congenital Ptosis with Report of 64 Cases Conforming to the Mendelian Rule of Dominance, *Trans. Am Ophthalmol Soc*, 16:255–276, 1918

[2] Arnold Sorsby, "Genetics in Ophthalmology," The C. V Mosby Company, St. Louis, 1951.

ing 10 or 15 per cent of the adult population. In most cases it is not apparent in the child's early years, but develops as he progresses through the elementary school The late onset has misled certain writers to the illogical conclusion that heredity is not a factor and that excessive use of the eyes in close work is the cause. This view is contradicted by the high concordance among identical twins and the low concordance among fraternal twins. Numerous pedigree studies, most of which were made in Europe, point unmistakably to heredity as a factor. In the great majority of families myopia behaves as a recessive; in some pedigrees dominance is indicated Alternative genetical explanations are expected in a complex functional trait

Farsightedness (Hyperopia)

This defect is the result of an eyeball so short that with the eye muscles relaxed, the parallel rays from distant objects are brought to a focus behind the retina The retinal image is therefore blurred. To correct for the abnormality the farsighted eye must constantly exert muscular effort —*the nearer the object the greater the effort necessary. Consequently* there is always more or less eyestrain unless glasses are worn. As an aggravating condition one eye is frequently more seriously affected than its mate

Hyperopia is much less common than myopia The symptoms appear in very young children. Although rather few genetical studies have been made, the evidence points to dominant heredity in most cases. An extreme form may be transmitted as a recessive

Astigmatism

In this defect there is a blurring of vision caused usually by a greater curvature of the cornea in one axis than in others. Special lenses are necessary to correct for this Astigmatism is often (though not necessarily) associated with farsightedness and may be more pronounced in one eye than in the other In most of the pedigrees studied astigmatism seems to be inherited as a dominant.

Cataract

One of the commonest types of eye defect which leads to *blindness is cataract, or opaque lens. Not all cataracts are hereditary, for* cataract may result from penetrating radiations as from the explosion of an atomic bomb, infection of the mother with rubella during the early months of pregnancy, diabetes, poisons, injuries, high temperatures, and malnutrition. Nevertheless, there are many cases which can be explained only on the hereditary basis

Different structural types of hereditary cataract are known. The age

at which the defect develops varies greatly, in some families it is present at birth; in others it comes on in childhood, at puberty, in middle age, or old age These facts suggest the presence of independent mutations Cataract—or the strong tendency to develop it at a certain age—is in nearly all cases inherited as a dominant character Recessive pedigrees, however, have been reported.

Glaucoma

Glaucoma is an extremely serious eye disease. Eye specialists tell us that in the United States it produces more blindness than any other single cause. Most of the cases develop in persons past forty years of age More than one-third of all blindness arising after this age is said to be due to glaucoma The immediate cause is faulty circulation of fluid inside the eyeball, resulting in a great increase in the internal pressure This destroys the head of the optic nerve, thus causing blindness Glaucoma is a striking example of an undoubted hereditary disease which can be controlled by surgery if it is taken in time The operation consists in opening up a channel for the circulation of fluid inside the eyeball Persons whose ancestors or near collateral relatives have had glaucoma should have periodical examinations by an oculist, since in many instances glaucoma cannot be detected by the patient himself before irreparable damage has been done The disease occurs more often in the small, farsighted eye than in the large, nearsighted eye

As in cataract, the age at which hereditary glaucoma develops varies considerably. In some families it may develop as early as at fifteen to twenty years of age The character is inherited as a dominant.

SKELETON AND MUSCLES

The skeletal and muscular systems may conveniently be considered together since both are closely related in development and are known to be affected by some of the same genes. Among these, the genes affecting body build and stature are of special interest.

Stature

Modern man shows great variation in stature, both with respect to individual differences and with respect to racial differences Fundamentally, racial differences and individual differences depend upon the same causes, since a race is a group of related individuals showing certain traits in common, each trait varying about its own mean Many genes are probably concerned in stature. The smallest races living today are the Pygmies· the Negritos of Africa and Asia The average stature of these people is between 4 and 5 feet, varying from one tribal group to another. Among

the shorter races not classed as Pygmies are the Lapps, the Bushmen of South Africa, the Eskimos, and the Japanese. At the opposite extreme are the Nordics, the Patagonians of South America, and certain African tribes, notably the Watutsi of Ruanda-Urundi in East Africa

The rate of growth, and perhaps the period over which growth continues, are affected by the glands of internal secretion, especially the



Figure 120. Three types of East Indian dwarfs, all more than 20 years of age, compared with a native of normal stature. (*A*) Cretin. (*B*, *C*) Midgets (ateliosis). (*D*, *E*) Chondrodystrophy. (*F*) Normal. (*From Rischbieth and Barrington, courtesy of Major, "Physical Diagnosis," W. B. Saunders Company*)

pituitary, the thyroids, and the gonads. Genes may act primarily upon these glands, which in turn modify growth One type of very tall individual with legs abnormally long in proportion to the trunk is apparently the result of underdevelopment of the gonads Eunuchs are said to have a similar type of body build. The common type of giant—usually seen in the circus—with excessively large hands and feet and a long jaw is the result of oversecretion of the pituitary gland Another type of growth disturbance leading to a particular kind of dwarf known as the cretin (Fig 120) is due to a deficiency of thyroxin from the thyroid gland. Cretinism

undoubtedly has a hereditary basis, although the exact mechanism has not been established.

There are also genes affecting growth independently of the glands Professor W. E. Castle found that rabbits of the breed known as Flemish giants grow more rapidly than small breeds, and that this difference is evident in the very early embryonic stages long before any of the glands of internal secretion are formed

It is an interesting fact that the proportions of the parts of the body are often somewhat different in tall and short persons, e g , the legs of short persons are relatively short as compared with the trunk, while the legs of tall persons are relatively long as compared with the trunk This holds true among the races, as illustrated by the comparatively short-legged Pygmies, Lapps, and Japanese, on the one hand, and certain long-legged African tribes, on the other. No doubt there are genes that affect the growth of the bones of arms, legs, and trunk independently One sometimes sees a tall man with relatively short arms and a short man with relatively long arms.

Chondrodystrophic Dwarfism

Most dwarfs belong to one or the other of two familiar types, the strong-man type and the midget (Fig. 120) In the former the limbs are much shortened and somewhat malformed The humerus and femur are especially short, the legs are usually bowed, and the individual walks with a waddling gait The arms cannot be straightened normally at the elbow; the fingers are short and are all of nearly the same length The trunk and head are of approximately normal size This type of dwarfism is technically known as *chondrodystrophy*, or *achondroplasia*, because of the imperfect development of the skeletal system Although the growth of the long bones is most severely affected, the shape of the head and facial features are often modified, and the trunk is sometimes deformed The mentality is apparently normal The writer once had dealings with three dwarfs of this type, a man and his two sisters, who for many years conducted a successful photographic studio Their intelligence seemed to be above average The man, who operated the camera, was especially successful in handling children Such dwarfs may be quite muscular. In circus troops they play the part of strong men

Many pedigrees of achondroplastic dwarfs have been published There is no doubt that the condition is inherited, but the exact mechanism has been much debated In a thorough study of the problem, Mörch,[1] of the University Institute for Human Genetics, Copenhagen, Denmark, presented pedigrees and other data indicating that it is inherited as a domi-

[1] E T. Mörch, Achondroplasia Is Always Hereditary and Is Inherited Dominantly, *J Heredity*, 31:439–444, 1940.

nant. A critical review of the literature convinced him that there are no reliable observations that contradict this theory. The numerous pedigrees showing a chondrodystrophic dwarf produced by normal parents he explains as the result of independent mutations. Studies of the trait in Denmark indicate that the rate of mutation is about one in 25,000 gametes.

Chondrodystrophic dwarfs are fertile and produce a 1:1 ratio of normal children and dwarfs The women usually are unable to give birth to living young except by Caesarean section, because of the contracted pelvis

Since a single dose of the gene is sufficient to produce the trait, we speak of it as a dominant But so far as is known, no one has yet seen a homozygote A double dose of the gene might well lead to a more extreme type of defect; it might even be lethal.

Ateliosis

The midget, or Tom Thumb type of dwarf (technically known as *ateliosis*, Fig. 120), has a very different appearance from the chondrodystrophic type, hence the midget type must be due to entirely different causes. The body may be essentially normal except for extremely small size. Growth is very slow, and the full stature, rarely exceeding 40 inches, is reached later than in normal persons. In adults, the head is relatively large and round rather than long The facial features are often noticeably infantile; and the limbs are somewhat shortened In many respects midgets resemble some of the African Pygmies, although they are smaller than Pygmies

Midgets are frequently fertile, sexual maturity, however, is much delayed. Most midgets are produced by normal parents. Cases also are known in which two midgets are the parents of a midget. The small pelvis usually makes Caesarean section necessary in childbirth. Midgets are of several distinct morphological types:[1] (1) an extremely rare "fetal-like midget" measuring about 30 to 36 inches in stature, (2) "true midgets," and (3) "miniatures." Miniatures seem to be essentially normal persons of unusually small stature. The various types probably have different genetic causes. In many pedigrees of ateliosis the best explanation is recessive inheritance McKusick[2] has given an interesting illustrated description of ateliosis in a Negro family. The parents of the dwarfs were cousins, normal in stature, although the father was only 61 inches tall. Recessive inheritance is indicated.

[1] C. W. Dupertuis, The Size and Proportions of Adult Midgets, *Am. J. Phys Anthropol.*, n s, 3:111-127, 1915

[2] V. A. McKusick, Primordial Dwarfism and Ectopia Lentis, *Am J. Human Genet.*, 7:189-198, 1955.

Extra Digits (Polydactyly)

A fairly common anomaly in man is the presence of extra fingers and toes. The extra digits usually consist of duplicated little fingers, little toes, thumbs, and great toes These may exhibit almost perfect development, or they may consist of minute imperfectly developed digits hanging by slender connections The metacarpal and metatarsal bones of hands and feet, respectively, corresponding to the extra digits, are sometimes duplicated, sometimes not, depending upon the size of the extra digits. Since the extra digits, if small, are usually removed by surgical operation during infancy, we are not aware of the actual frequency of this condition.

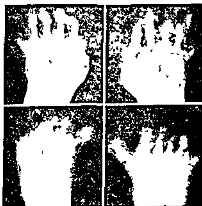


Figure 121. X-ray photograph of hands and feet of baby, showing six fingers on each hand and seven toes on each foot No metacarpal bone for the extra little finger is visible and no metatarsal bone for the extra little toe, although there is one for the extra big toe (*From McClintic, J Heredity*)

Polydactyly is usually inherited as a dominant Brown S. McClintic gives an interesting pedigree accompanied by X-ray pictures of a polydactylous mother and her baby (Figs. 121 and 122), showing inheritance of the deformity through five generations.[1] The affected members of this family usually had six fingers on each hand and seven toes on each foot. From six matings in this pedigree, in which one parent was polydactylous, 13 children had extra fingers and toes and 12 were normal The 1 1 ratio fits the theory of a single dominant gene Other aspects of the pedigree agree perfectly with this explanation Some pedigrees of polydactylism indicate dominance with reduced penetrance.

Short Fingers and Toes (Brachydactyly)

In this condition a single gene acting as a dominant interferes with the normal development of the long bones In the common form of brachydactyly all the digits of the hands and feet, except the thumbs and great toes, appear to lack one joint. This appearance is in reality due to the marked reduction of the middle joint accompanied frequently by its fusion with the distal one (Fig. 123) The thumbs and great toes have the normal number of joints, but the basal joint is greatly reduced in length

[1] B S. McClintic, Five Generations of Polydactylism, *J Heredity*, 26:141-144, 1935.

The arms and legs also are shorter than normal. Brachydactylous men are shorter than their normal brothers, and brachydactylous women are shorter than their normal sisters.

Brachydactyly was the first human characteristic shown to follow Mendel's laws. The earliest pedigree was published by W. C Farabee[1] in 1905, for a family in Pennsylvania in which the abnormality was traced through five generations without a break (Fig. 124). In matings between



Figure 122. X-ray photograph of feet of the mother of the baby whose hands and feet are shown in Fig 121. Note that in both mother and baby the metatarsal bones of the extra (inner) big toes are abnormal in position. (*From McClintic, J. Heredity.*)

persons with brachydactyly and normal persons, he reported 36 brachydactylous offspring to 33 normal offspring. This 1:1 ratio would be expected from a backcross of a hybrid dominant to a recessive. No marriages between two brachydactylous persons were reported by Farabee.

Subsequent studies of other families have confirmed the inheritance of brachydactyly as a single dominant Several other types of brachydactyly have been discovered, in which one or more definite digits is always involved. These also are dominant A brief classification of hereditary finger defects is given by Professor Iltis in the paper from which the X-ray photographs shown in Fig. 123 have been taken [2]

Split Hand and Foot (Syndactyly)

A somewhat rare abnormality of hands and feet, sometimes called "lobster claw," has been studied and described in different races from

[1] William C. Farabee, "Inheritance of Digital Malformations in Man," Papers of the Peabody Museum, vol. 3, no. 3, Harvard University, Cambridge, Mass., 1905.
[2] Hugo Iltis, A New Case of Typical Brachydactyly, *J. Heredity*, 35:145–148, 1944.



Figure 123. Brachydactylous hands of mother (*above*) and daughter (*below*) Note marked reduction of middle joint of ring finger and middle finger of the mother's left hand On her right hand all middle joints are fused to distal ones except on the middle finger (*From Illis, J Heredity*)

widely separated countries. It has probably arisen independently several times by mutation. In all cases it is inherited as a dominant. The condition is variable in its expression within a single family. Occasionally it varies on the two sides of the same person, which indicates that its development may be modified by subtle environmental differences during embryonic life. There is sometimes a thumb and only one large finger —the latter indicating the fusion of several digits—with a similar

tion of the feet More often there are four digits, with a deep cleft where the middle finger or toe should be

In some families the feet alone or the hands alone are affected John C. Wightman[1] has published an extensive pedigree of syndactyly in a family in this country, with a review of earlier reports.

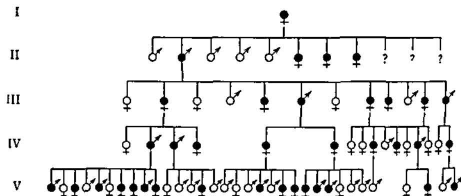


Figure 124. Pedigree of affected members of Farabee's brachydactylous family. Ratio 36 affected 33 normal, almost a perfect ratio as expected from backcross matings

Numerous other types of hereditary abnormality of hands and feet involving shortening, fusing, malformation, etc, are described by Professor Gates in his book already referred to.

Harelip and Cleft Palate

Harelip and cleft palate, either alone or together, are among the commoner congenital abnormalities in man. These defects develop during the second month of embryonic life, when the upper lip consists of two lateral and one middle portion and the upper jaw and roof of the mouth each consist of two lateral halves. Normally these separate portions gradually grow together. In normal persons the depression on the upper lip (philtrum) and the white line on the roof of the mouth, readily visible with a mirror, indicate the lines of fusion. A failure of fusion results in a split on one or both sides of the lip, known as harelip, or a split in the roof of the mouth, cleft palate.

An analysis of practically all of the cases of harelip and cleft palate born to mothers of Birmingham, England, in the years 1940–1950 has recently been published[2] There were 285 cases among 218,693 births, or

[1] J. C Wightman, A Pedigree of Syndactyly, *J. Heredity*, 28:421–423, 1937.

[2] Brian MacMahon and Thomas McKeown, The Incidence of Harelip and Cleft Palate Related to Birth Rank and Maternal Age, *Am. J. Human Genet*, 5:176–183, 1953.

1.30 per thousand births. The nature of the malformation and sex of those affected was as follows.

Type	Number	Sex
Harelip	66	60 6% male
Harelip and cleft palate	105	59 0% male
Cleft palate	114	41 2% male

It was found that harelip, and harelip associated with cleft palate, were unrelated to birth rank, but increased with maternal age (from 0 37 per 1,000 births at ages under 23 to 1 41 per 1,000 at ages 38 and over) Cleft palate without harelip seemed to be independent of both maternal age and birth order. These results are consistent with earlier studies indicating that harelip and harelip with cleft palate are genetically unrelated to cleft palate not associated with harelip

A number of pedigrees have been published showing the recurrence of harelip and harelip with cleft palate in several consecutive generations These pedigrees suggest a dominant gene In other pedigrees, however, both parents are apparently normal The exceptions may have their explanation in the great variability in expression of the gene or in incomplete penetrance A new mutation may, of course, occur now and then.

Cleft palate alone seems to behave as an irregular dominant, it is less common in males than in females

In mice, harelip is hereditary and, as in man, is found more often in males than in females and more frequently on the left side than on the right. Grüneberg[1] states that there is no doubt that more than one gene is involved in mice; he thinks that there is a small number of cumulative genes, none of which by itself is able to produce harelip In his opinion, however, the question of the mode of inheritance is not definitely settled

Intrauterine environmental factors seem to be important in the development of harelip in mice as well as in men In mice the development of harelip decreases with increasing age of the mother, just opposite to the situation in man. The injection of cortisone and hormones from the anterior lobe of the pituitary into pregnant mice is reported to increase the frequency of harelip in the offspring

Miscellaneous Skeletal Defects

Many other skeletal abnormalities which seem to have some hereditary basis have been described. In some, the Mendelian mechanism is clearly indicated The problem may be complicated by the important influence

[1] Hans Grüneberg, "The Genetics of the Mouse," 2d ed, Martinus Nijhoff, The Hague, 1952

of the environment. Among the characters that have been described as Mendelian or as having some genetic basis are these: clubfoot, flat foot, knock-knees, bowlegs, double-jointedness, congenital dislocation of the hip, arthritis deformans, absence of the kneecap, cartilaginous and bony outgrowths (exostoses), prominant lower jaw (prognathism), pinhead (microcephaly), absence of collarbones with skull abnormality, brittle bones, funnel breast, lateral curvature of the spine, "round back," skull shape, height of cheekbones, etc.

Rupture (Hernia)

Comparatively few abnormalities of the muscular system are known to exist, and in only a few cases have they been shown to be Mendelian in character. Rupture is a defect in which heredity undoubtedly plays a part. According to Dr Lenz,[1] about one in every 20 or 30 men is ruptured, as compared with only about one in 150 women.

The striking difference in the frequency of rupture in men and women depends partly upon the nature of the work of the two sexes, since the strain of lifting heavy objects is a factor. But the anatomical differences in the sexes probably is more important. In the male the testes develop within the abdominal cavity and are forced downward gradually between the muscles of the lower abdomen, finally coming to lie outside the abdominal cavity in a sack called the scrotum. This migration usually occurs before birth. The passageway through the body wall is known as the inguinal canal. The muscles normally close around the canal, leaving only sufficient room for the passage of the sperm duct, nerves, and blood vessels of the testes. In case the muscular wall around the canal is weak or imperfectly formed, a loop of the intestine may be forced into the canal and through the body wall, forming a bulge under the skin in the region of the groin. This condition is known as an inguinal hernia. The descent of the testes, therefore, plays a part in the high frequency of this type of hernia in males.

Lenz concludes that hernia unmistakably runs in families and suggests that it is dominant, although he gives no pedigrees. West[2] published two instructive pedigrees showing the frequent recurrence of hernia through three and five generations, respectively. In these pedigrees a number of the individuals were born with hernia, but in most cases it was brought on as a result of some physical exertion. In these families it seems clear that a weakness of the abdominal wall was inherited, probably as a domi-

[1] Erwin Baur, Eugen Fischer, and Fritz Lenz, "Human Heredity," transl by Eden and Cedar Paul, The Macmillan Company, New York, 1931.

[2] L. S. West, Two Pedigrees Showing Inherited Predisposition to Hernia, *J. Heredity*, 27:449–455, 1936.

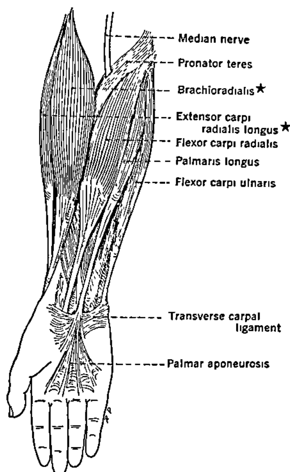


Figure 125. The more superficial flexor muscles of the right forearm (except those that are starred, which are extensors), showing the position of the highly variable palmaris longus (*From Hollinshead, "Functional Anatomy of the Limbs and Back," W. B Saunders Company*)

nant, and that occasionally a person with the inherited tendency escaped developing a hernia

Weimer[1] has published a pedigree covering four successive generations showing congenital double inguinal hernia in males His data are in agreement with previous studies in support of the theory of dominant sex-influenced heredity.

[1] B R Weimer, Congenital Inheritance of Inguinal Hernia, *J Heredity*, 40.219–220, 1949

The frequency with which both members of a pair of identical twins—necessarily of the same heredity—have ruptures is evidence for its hereditary basis

Long Palmar Muscle Absent

The *long palmar* is one of the superficial muscles of the forearm It is inserted on the palm of the hand and serves to flex the wrist Its presence or absence can be studied on living persons by observing the tendons on the palm side of the wrist (Fig. 125) Thompson, McBatts, and Danforth[1] found from examination of a large number of white families that this muscle was missing in about 16 per cent of males and 24 per cent of females They concluded that absence of the palmaris longus was inherited as a dominant.

Numerous more recent studies by other investigators support these general findings Among whites, 10 to 25 per cent lack the muscle on one or both sides, the percentage varies with the national group examined In Negroes it is missing in about 5 per cent; in Mongoloids in 2 5 to 5 per cent, excepting a group of Penobscot Indians, among whom Thompson et al. found 19 3 per cent absence. Spuhler[2] has summarized the data from various workers. Pedigree studies point to dominant inheritance of absence of the muscle, with incomplete penetrance of the gene, and variability in its expression on the two sides of the body.

PROBLEMS

1. Distinguish between the terms *congenital trait* and *hereditary trait*
2. Account for the tendency of mutations to be unadaptive
3. List some of the special difficulties involved in the study of human heredity as compared with heredity in domesticated animals.
4. List several Mendelian differences in man that you regard as normal differences
5. Why is the genetic analysis of characters like stature and skin color especially difficult in man?
6. How do you account for the fact that in published lists of human traits the mutant types are more often dominant than recessive, while in most other mammals the recessives exceed the dominants in number?

[1] J. W. Thompson, J. McBatts, and C. H Danforth, Heredity and Racial Variation in the Musculus Palmaris Longus, *Am J Phys. Anthropol*, 4:205–218, 1921

[2] James N Spuhler, Some Genetic Variations in American Indians, in W S. Laughlin (ed), "The Physical Anthropology of the American Indian," pp 177–201, Viking Fund, New York, 1951.

16

HEREDITY IN MAN. II

In this chapter we conclude the systematic treatment of human hereditary characteristics begun in the preceding chapter Traits chosen as examples are listed in Table 21.

CIRCULATORY AND RESPIRATORY SYSTEMS

The circulatory system is the seat of a number of hereditary defects and diseases, one of the best known being the sex-linked disease hemophilia, discussed in Chap 10 Heredity is an important factor in susceptibility to allergic and parasitic diseases, and these commonly involve the circulatory and respiratory systems. Normal hereditary differences in the circulatory system are also well established, the most important of which are the chemical differences that account for the large number of blood groups or blood types found among individuals In Chap 7 we described two series of blood groups, the A-B-O and the M-N-S series Numerous others have been discovered in recent years We shall consider here in some detail one of the newer and most interesting of these—the Rh series

The Rh-Hr Blood Types

In 1940 Landsteiner and Wiener[1] reported the discovery of a new and, as subsequent events have demonstrated, very important difference in human bloods Using a serum obtained from rabbits immunized with the blood of a rhesus monkey, they found that the antibodies in the serum agglutinated not only the red corpuscles of the rhesus monkey but also those of about 85 per cent of white persons The other 15 per cent gave no reaction. They accordingly designated the former persons as Rh-positive and the latter as Rh-negative.

From tests of 60 families, including 237 children, the discoverers concluded that the Rh substance, an agglutinogen, was inherited as a dominant. Later studies of 40 additional families by Wiener and Sonn confirmed this theory. Two Rh-negative parents produced only Rh-negative

[1] K. Landsteiner and A. S. Wiener, An Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood, *Proc. Soc Expt. Biol. Med.*, 43:223, 1940

TABLE 21. MENDELIAN CHARACTERISTICS IN MAN*
(Arranged in the order in which they are considered in the text)

Dominant	Recessive	Page
CIRCULATORY AND RESPIRATORY SYSTEMS		
Rh-positive blood type	Rh-negative	343
Hemolytic jaundice	Normal	351
Nosebleed and blood cysts (telangiectases)	Normal	352
Varicose veins and hemorrhoids	Normal	352
Normal—dominance incomplete	Allergy	352
Resistance to tuberculosis—multifactorial	Susceptibility to tuberculosis	353
EXCRETORY SYSTEM		
Polycystic kidney	Normal	355
ENDOCRINE GLANDS		
Normal (some uncertainties)	Diabetes mellitus	355
Diabetes insipidus	Normal	356
DIGESTIVE SYSTEM		
Normal	Pyloric stenosis	357
Ulcers (mode of inheritance uncertain)		357
REPRODUCTIVE SYSTEM		
Hypospadias—irregular expression	Normal	358
CANCERS AND OTHER MALIGNANT TUMORS		
Normal	Xeroderma pigmentosum	360
Von Recklinghausen's disease	Normal	361
Cancer of colon	Normal	362
Cancer of eye (retinoblastoma)	Normal	364
NERVOUS SYSTEM		
Taste for phenylthiocarbamide	Nontaste for PTC	365
Normal	Congenital deafness	368
Otosclerosis	Normal	368
Normal (mild type dominant)	Muscular atrophy	368
Normal	Spinal ataxia	369
Paralysis agitans	Normal	370
Normal	Epilepsy (?)	370
Huntington's chorea	Normal	373
Normal	Microcephaly	376
Normal	Amaurotic idiocy	378
Normal	Schizophrenia	378
Manic-depressive psychoses	Normal	381
SPECIAL TALENTS (mode of inheritance uncertain)		
Musical ability		382
Ability in drawing, painting, sculpture		384
Mathematical ability		385

* *See also Table 20, page 307.*

children, as theory demands of a recessive The other possible matings, positive by positive and positive by negative, also agreed in the expected ratios of Rh-positive and Rh-negative offspring produced.

A knowledge of the Rh agglutinogens (several are now known) is of great practical importance because of their role in the causation of a disease known as erythroblastosis in the fetus and newborn infant This disease develops only in an Rh-positive infant whose mother is Rh-negative



Figure 126. Karl Landsteiner, 1868–1943. (*Courtesy of Dr Alexander S. Wiener.*)

and whose father is necessarily Rh-positive. The Rh-positive fetus produces the agglutinogen on its red corpuscles These may pass through the placenta into the mother's blood and stimulate in her body the production of antibodies against the Rh-positive corpuscles of the fetus (Fig 127) These antibodies in turn pass through the placenta from mother to the fetus and cause the destruction of fetal red corpuscles, which may be so extensive as to cause the death of the fetus and so a stillbirth. Sometimes the destructive effect appears only after birth. Affected babies show severe anemia, jaundice, and edema, with enlargement of the spleen

and liver. Only a minority of cases recover spontaneously. By the use of exchange transfusions, whereby the baby's blood is withdrawn and replaced by Rh-negative blood, more than 90 per cent of these babies can be saved

Shortly after the discovery of the Rh blood types, Wiener and others found that there was more than one variety of the Rh agglutinogen. These discoveries stimulated a great deal of research, which has continued down to the present time Investigators in this country and abroad

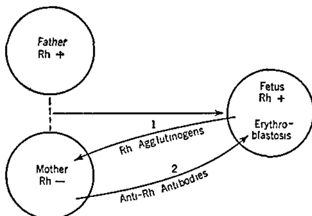


Figure 127. Diagram showing the kind of mating that may result in erythroblastosis.

have published well over a thousand papers and books on the Rh-Hr types

The list of variants of the Rh agglutinogen and their corresponding antibodies has grown steadily to more than a dozen The original form of the agglutinogen discovered by Landsteiner and Wiener, however, has proved to be much the most antigenic and the most important practically, since it is responsible for over 90 per cent of the cases of erythroblastosis

Fortunately, erythroblastosis is much less common than one would expect on the basis of the frequency of marriages between Rh-negative women and Rh-positive men What is the expected frequency of erythroblastosis among infants? This may be readily calculated if we know the proportions of Rh-positive men who are homozygous and heterozygous, respectively These proportions are easily calculated by using the Hardy-Weinberg law, described on page 285 Since 0 15 of men are Rh-negative, the frequency of the Rh-negative gene r is $\sqrt{0\ 15} = 0\ 39$ Hence the frequency of the Rh-positive allele R is $1 - 0\ 39$, or $0\ 61$. Applying the Hardy-Weinberg rule, we calculate the three possible genotypes in the population as follows·

$$(0\ 61\ R + 0\ 39\ r)^2 = (0\ 61)^2\ RR + 2(0\ 61 \times 0\ 39)\ Rr + (0\ 39)^2\ rr,$$

or 0 3721 RR + 0 4758 Rr + 0 1521 rr These proportions apply to both males and females.

The expected matings between Rh-positive men and Rh-negative women, with their expected offspring, are therefore as follows.

Matings	Offspring	
	Rh-positive	Rh-negative
0 3721 RR men × 0 1521 rr women = 0 057	0 057	
0 4758 Rr men × 0 1521 rr women = 0 072	0 036	0 036
Total	0 093	0 036

Our calculation shows that 9 3 per cent of all embryos in the population are thus genetically and environmentally vulnerable Of these vulnerable embryos only a small percentage actually develop the disease Potter[1] states that of the 22,742 births at Chicago Lying-In Hospital, 1940 to 1946, 0 4 per cent were affected This is only 4 3 per cent of those expected Several reasons may be given for this fortunate escape (1) the first-born child is not often affected, unless the mother has at some time had a transfusion of Rh-positive blood or an abortion of an Rh-positive embryo, (2) some special uterine condition may be necessary for the passage of red blood corpuscles from embryo to mother, (3) certain women may never develop antibodies against the Rh agglutinogens even though exposed to them

Coming back to the genetics of the Rh types, we find that a dozen or more different forms of the Rh agglutinogen have been reported Wiener holds that each of these is due to a different allele of a gene at a single locus on one of the autosomes Race[2] and his coworkers and R A Fisher, in England prefer the theory of three closely linked genes, each with a series of alleles From the purely Mendelian point of view we have seen in our discussion of the M-N-S types that a single gene is transmitted in the same manner as two or more completely linked genes If there really are three Rh genes, the linkage seems to be complete, since no crossing over has been observed, so far as transmission is concerned we can therefore just as well speak of one gene producing a complex agglutinogen The analysis of pedigrees and gene frequencies in populations seems to fit the theory of a single series of alleles

The terminology for Rh is naturally troublesome because the various

[1] Edith L Potter, "Rh . . Its Relation to Congenital and Hemolytic Disease and to Intragroup Transfusion Reactions," Year Book Publishers, Inc, Chicago, 1947

[2] R R. Race and Ruth Sanger, "Blood Groups in Man," 2d ed , Charles C Thomas, Publisher, Springfield, Ill , 1954.

agglutinogens cannot be described by their specific chemical constitutions, which are unknown, they are identified only by their reactions with specific immune sera We therefore need two sets of arbitrary symbols, one set for the allelic genes and one for the corresponding agglutinogens These two sets of symbols should be so related to one another as to ensure ease and certainty of identification

TABLE 22 THE RH SERIES OF ALLELIC GENES*
(Symbols proposed by R. A Fisher, in parentheses)

Genes	Gene frequencies among New York City Caucasoids (per cent)	Corresponding agglutinogens	Reactions with Rh serums†			Reactions with Hr serums†		
			Anti-Rh_0	Anti-rh′	Anti-rh″	Anti-Hr_0 (hypothetic)	Anti-hr′	Anti-hr″
r(cde)	38 0	rh	−	−	−	+	+	+
r′(Cde) .	1 4	rh′	−	+	−	+	−	+
r″(cdE)	0 5	rh″	−	−	+	+	+	−
r^y(CdE)	0 01	rh_y	−	+	+	+	−	−
R^0(cDe)	3 2	Rh_0	+	−	−	−	+	+
R^1(CDe)	40 4	Rh_1	+	+	−	−	−	+
R^2(cDE)	16 4	Rh_2	+	−	+	−	+	−
R^z(CDE)	0 1	Rh_z	+	+	+	−	−	−

* From Wiener

† The individual's phenotype is the result of the action of a pair of genes, e g, genotype R^1R^2, etc The effect of a single gene can be inferred, however, from the study of homozygous individuals. In the case of the rare genes r', r'', R^z, and r^y, where homozygous individuals are not available, the effect of the individual gene is determined by deduction

An important physiological and genetical fact must be kept in mind: each allele is dominant in the sense that if present in even a single dose, its agglutinogen develops Therefore one parent or the other always has an agglutinogen if this is present in a child.

Table 22 from a recent book by Wiener[1] shows the eight most common Rh alleles among Caucasoids, their corresponding agglutinogens, and the antibodies with which they react positively. Several points are worth noting in this table

The antiserums, which contain the antibodies, are divided into two subclasses called Rh and Hr. In homozygous individuals where there is a positive reaction (+) with a serum in one subclass there is no reaction (−) with the corresponding serum in the other subclass. This reciprocal,

[1] Alexander S. Wiener, "An Rh-Hr Syllabus: The Types and Their Applications," Grune & Stratton, Inc., New York, 1951

or allelic, relationship holds throughout, although in the case of the anti-Hr_0 serum (not yet obtained) the reactions are hypothetical A single agglutinogen, as the term is used by Wiener, may have one, two, or three different factors and hence may react with as many serums A heterozygous individual may show a positive reaction with as many as all six of the serums given in Table 22 R^zr (*CDE*/*cde*) is an example of such a

TABLE 23 THE RH-HR BLOOD TYPES AND THEIR CORRESPONDING GENOTYPES USING THE SIX MOST ABUNDANT ALLELES*

Rh blood types	Reaction with serum		Rh subtypes	Approximate frequency in New York City, %	Possible genotypes
	Anti-hr′	Anti-hr″			
rh	+	+	rh	13 0	rr
rh′	−	+	rh′rh′	01	$r'r'$
rh″	+	+	rh′rh	1 0	$r'r$
	+	−	rh″rh″	005	$r''r''$
rh′rh″	+	+	rh″rh	0 5	$r''r$
	+	+	rh′rh″	01	$r'r''$
Rh_0	+	+	Rh_0	2 0	R^0R^0 and R^0r
Rh_1	−	+	Rh_1Rh_1	20 0	R^1R^1 and R^1r'
Rh_2	+	+	Rh_1rh	34 0	R^1r, R^1R^0, and R^0r'
	+	−	Rh_2Rh_2	3 0	R^2R^2 and R^2r''
Rh_1Rh_2	+	+	Rh_2rh	12 0	R^2r, R^2R^2, and R^0r''
	+	+	Rh_1Rh_2	14 5	R^1R^2, R^1r″, and r′R^2

* From Wiener.

genotype In Fisher's terminology each letter represents an agglutinogen as well as its conditioning gene

The alleles represented by capital R's on the four bottom rows in Table 22 are those responsible for Rh-positive persons Such persons all have the originally discovered Rh_0 factor, they may also have the rh′ or the rh″ factor, or both. Genes represented by small r's are responsible for Rh-negative persons.

Genes R^z and r^y were recently discovered Both are very rare—R^z, one in 1,000, and r^y, one in 10,000 The frequencies of the genes must not be confused with the frequencies of the types (phenotypes); the latter are observed directly by the agglutination tests (Table 23)

As Tables 22 and 23 indicate, the Rh genes present in individuals classed as Rh-negative also produce agglutinogens. The antibodies for these have been given symbols with the letters reversed: anti-hr′ and anti-hr″—as already mentioned, anti-Hr_0 is not yet available. Clinically these antibodies are of minor importance since they are rarely induced by blood transfusions or as a result of pregnancy.

Up to now 14 Rh agglutinogens have been reported These, with gene symbols, are listed by Wiener[1] and his coworkers All are regarded as alleles of the original As mentioned above, English investigators prefer to represent the *Rh* genes as occupying three neighboring loci on a chromosome; this means three sets of alleles Race and Sanger state that no

TABLE 24 RH GENE FREQUENCIES IN DIFFERENT HUMAN POPULATIONS*

Populations	Investigators	Number of persons tested	Calculated frequencies, %, of genes						
			r	r'	r''	R^0	R^1	R^2	R^z
Caucasoids·									
U S A	Wiener et al	2,390	36 65	1 23	0 52	3 73	42 70	15 06	0 05
U S A	Unger et al.	7,317	38 3	1 4	0 8	2 8	42 1	15 1	—
England	Race et al.	2,000	38 86	0 98	1 19	2 57	42 05	14 11	0 24
Canada	Chown et al	3,100	39 55	1 24	0 73	1 91	43 48	12 87	0 22
Spain	Race et al	223	36 95	0	0 61	0 61	50 11	12 16	0 45
Czechoslavakia	Raska et al.	181	40 02	0 69	0 69	1 36	39 59	16 90	0 75
Basques	Chalmers et al	383	53 16	1 47	0 25	0 50	37 56	7 07	0
Negroids, N Y C	Wiener et al	223	24 4	2 7	0	42 1	11 7	14 4	0
	Wiener et al	200	27 39	0 89	0 89	43 32	17 30	9 02	0
Pygmies, Belgian Congo	Hubinont and Snoeck	94	10 5	0	0	63 2	6 2	19 5	0
Siamese	Phansanboom et al.	213	0	0	0	11 13	75 54	11 13	2 16
Papuans	Simmons and Graydon	100	0	0	0	2 1	94 3	2 0	1 6
Australian Aborigines	Simmons and Graydon	234	0	12 87	0	8 54	56 42	20 09	2 08
New Caledonians	Simmons *et al.*	325	*0*	*0*	*0*	*5 48*	*83 32*	*10 77*	*0 43*
Mexican Indians	Wiener et al	98	0	0	0	5 8	64 1	26 8	3 3
Navaho Indians	Boyd and Boyd	305	0	17 31	2 02	8 37	31 05	35 33	5 7

* From Wiener

cases of crossing over have been observed; also that the frequencies of the eight "chromosomes" or combinations are not such as to indicate crossing over. They believe that "linkage is very close, perhaps even absolute." If there is no crossing over we may therefore think of the three letters *CDE* as representing a single gene having several effects This concept is fundamentally the same as Wiener's

[1] A. S. Wiener, Eve B Gordon, and Laura Cohen, A New Rare Rhesus Agglutinogen, *Am. J. Human Genet*, 4 363–372, 1952

As in the case of the A-B-O and the M-N-S groups we find interesting racial differences in the frequencies of the Rh types Expressed in gene frequencies the differences for some of the racial and national groups tested are shown in Table 24 It is apparent that Mongoloids and some other Oriental peoples tend to be entirely Rh-positive Tests of Chinese and Eskimos are almost 100 per cent Rh-positive also The Basques, a somewhat isolated group of Caucasoids living in the mountains bordering Spain and France, have the highest frequency of gene *r* (about 28 per cent negative) of any sizable group of people yet studied Some anthropologists consider the Basques survivors of a human stock once widely dispersed in Europe.

Other agglutinogens have been found from time to time in the blood of human beings, usually by following up an unexpected reaction after a blood transfusion The frequency with which these are being reported indicates that there may be many such—no one knows how many actually exist. The genetic principles involved in these agglutinogens are essentially the same as in the A-B-O, M-N-S, and Rh-Hr series, consequently there would be no point in listing or describing them here For an excellent recent summary of these the reader is referred to Race and Sanger's "Blood Groups in Man," previously cited

Most of the series of blood groups and blood types so far analyzed are inherited independently of the others linkage has been demonstrated between two series known as Lewis, and Lutheran

Hemolytic Jaundice

Jaundice is an abnormal condition in which there is a visible accumulation of the yellowish bile pigment in the skin and whites of the eyes It is sometimes the result of an obstruction of the bile duct by gallstones or infections, so that the dammed-up bile is forced into the blood.

In hemolytic jaundice, as the name indicates, there is an excessive destruction of the red corpuscles, leading to anemia The hemoglobin thus released is in part converted into bile pigment by the liver The blood picks up the pigment, carries it over the body, and deposits it in certain tissues In hemolytic jaundice the spleen, which may become enlarged, is the site of corpuscle destruction The removal of the spleen by operation has frequently produced good results

Among the early symptoms that can be detected in the laboratory are microcytosis (abnormally small red blood cells), reticulocytosis (increased number of reticulocytes, red blood cells with a network indicating immaturity of cells), and increased fragility of red corpuscles in hypotonic salt solution. Pedigrees show that hemolytic jaundice is inherited as a dominant, with great variability in its expression

Nosebleed with Blood Cysts (Telangiectasia)

According to Cockayne, the first indication of the presence of this vascular defect is repeated and serious nosebleed, which may begin in childhood, at puberty, or not till early adult life and which often becomes more frequent and more severe as time passes In some individuals nosebleed is the only symptom, but in most cases this is followed by the development of hard, red, wartlike spots in the skin, especially about the face and hands and on the lips, tongue, and nasal mucous membrane These red spots, which usually vary in diameter from 2 to 10 mm , consist of swollen blood vessels, caused by the lack of muscular and elastic tissue in the walls of small arteries Hemorrhages often result from the rupture of the swollen vessels, sometimes with fatal results Many pedigrees have been published, which indicate a clear-cut case of dominant inheritance It is reported that estrogen, a female sex hormone, is a very effective remedy (*J. Heredity*, July–August, 1952, p 192).

Varicose Veins and Hemorrhoids

Veins sometimes become greatly swollen, elongated, and tortuous in their course and are then known as varicose veins. The superficial veins of the legs are most often affected Varicose veins in the rectum are known as hemorrhoids. Varicose veins in the legs seem to result from defective valves, which normally prevent the backward flow of blood in the veins. The veins in the rectum have no valves; consequently, hemorrhoids result merely from dilation.

The activities of the individual undoubtedly influence onset and severity of the symptoms Any occupation requiring heavy lifting, long hours of standing on the feet, or activity otherwise retarding the circulation in the legs throws an added strain upon the veins of the legs, thus favoring development of varicose veins Childbearing is an important factor. Sedentary occupations predispose to hemorrhoids. A hereditary factor is indicated, however, by the tendency for hemorrhoids and varicose veins to run strongly in families and by the fact that varicose veins are always concordant in one-egg twins [1] Many persons subjected to all of the predisposing conditions never develop the defects; hence they probably lack the hereditary factor The tendency to varicose veins is dominant.

Allergy

Allergy is the term used to denote the peculiar sensitivity exhibited by certain persons to specific foods and foreign substances, usually proteins. In an individual who is naturally susceptible, an exposure to the sub-

[1] Tage Kemp, "Genetics and Disease," Oliver & Boyd, Ltd , Edinburgh and London, 1951.

stance results in an antigen-antibody reaction This reaction expresses itself in a variety of symptoms and conditions, such as eczema, hives, asthma, and hay fever.

The capacity to become sensitized is inherited as an irregular dominant, while early, severe allergy seems to require a double dose of the gene Since sensitization depends upon exposure to a certain dosage of the offending allergen, not everyone who bears the gene may develop the symptoms There is high concordance of allergic reactions in identical twins, but not perfect concordance with respect to the specific substance to which they react. In some pedigrees the affected individuals are all allergic to the same substances and develop the same symptoms, while in other pedigrees there is considerable variation in these respects The age at which allergy appears is variable

Resistance to Tuberculosis

There are many lines of evidence which prove beyond reasonable doubt that people differ in their natural or inherited resistance to various infectious diseases. Some of these differences are correlated with racial differences Thus the Negro is more resistant to scarlet fever, measles, erysipelas, malaria, yellow fever, and diphtheria than the white man, but less resistant to tuberculosis and pneumonia [1] In making such comparisons one must always be on guard to recognize the other factor of resistance, namely, the environment and general living conditions, but when people living under practically identical conditions show marked differences in their resistance to specific infections, as is often the case, we can only conclude that heredity probably is a factor An excellent exhaustive study of racial differences in susceptibility to diseases is found in a book by Dr. Julian Lewis, pathologist at the University of Chicago.[2]

It is not possible at present to say how important such environmental conditions as food, shelter, dust, and extent of exposure to the bacillus of tuberculosis may be as compared with the natural resistance of the individual Nor can we give the number of genes involved or the exact mode of inheritance What evidence exists seems to indicate that high resistance is dominant, and susceptibility is recessive

Instructive on this point is a series of controlled experiments on guinea pigs performed by Wright and Lewis[3] in which 412 animals were inoculated with tuberculosis germs in order to discover how long they could

[1] Samuel J Holmes, "The Negro's Struggle for Survival. A Study in Human Ecology," University of California Press, Berkeley, 1937.

[2] Julian Herman Lewis, "The Biology of the Negro," University of Chicago Press, Chicago, 1942

[3] Sewall Wright and P. A. Lewis, Factors in the Resistance of Guinea Pigs to Tuberculosis, with Especial Regard to Inbreeding and Heredity, *Am. Naturalist*, 55:20–50, 1921.

survive the infection. Nearly half the animals were from five distinct and homogeneous inbred lines, the rest were crossbred animals There was much variability in resistance within each inbred line; nevertheless a striking difference was found among the inbred lines themselves. In various crosses between individuals of two inbred lines, resistance proved to be dominant over susceptibility, and in some cases the hybrids were even more resistant than either parental line. No attempt was made to estimate the number of genes concerned in resistance and susceptibility to tuberculosis

In man, Professor Raymond Pearl[1] published studies on the frequency of tuberculosis in a total of 564 matings producing 2,480 offspring He found that when both parents have tuberculosis the child is about 4 3 times as likely to have tuberculosis as when neither parent is affected. With one parent affected the child is about 1.7 times as likely to have it as when neither parent is tuberculous One might naturally conclude that these differences are the result of greater opportunities for infection in families with one parent or both infected, but Pearl concludes from his analysis that in the cases studied the differences in heredity are the only factors which play a significant role in the result Quoting from Pearl:

> The regular increase in the offspring percentage incidence as the amount of parental tuberculosis increases seems impossible of rational explanation on any other basis than that of hereditary influence Increasing chance of massive contact infection in the home cannot reasonably explain it, in the opinion of clinicians whom we have consulted about these results. For plainly the chance of clinical tuberculosis resulting from such contact infection when both parents are tuberculous is nothing like quantitatively double what it is when only one parent is tuberculous. Yet the offspring incidence in this case is more than double. Nor does it seem probable that a child with one parent in the home actively tuberculous is only 1 7 times as likely to develop clinical tuberculosis as a child with no tuberculous parent The risk seems probably greater than this

Studies of the frequency of tuberculosis in twins—identical twins versus fraternal twins—also lead to the conclusion that heredity plays an important role in the development of tuberculosis [2,3] According to studies made by Kallmann,[4] the concordance of one-egg twins for pulmonary

[1] R. Pearl, On the Incidence of Tuberculosis in the Offspring of Tuberculous Parents, *Z. Rassenkunde,* 3:3, 1936

[2] Karl Diehl and O. F. v. Verschuer "Zwillingstuberkulose I" (reviewed in *J. Heredity,* January, 1934), 1933; "Zwillingstuberkulose II" (reviewed in *J Heredity,* March, 1937), Gustav Fischer Verlagsbuchhandlung, Jena, Germany, 1936.

[3] Ruth Price Puffer, "Familial Susceptibility to Tuberculosis," Harvard University Press, Cambridge, Mass , 1944.

[4] Franz J Kallmann, "Heredity in Health and Mental Disorder," W W. Norton & Company, Inc , New York, 1953

tuberculosis is about 85 per cent and for two-egg twins and sibs about 25 per cent.

EXCRETORY SYSTEM

A number of diseases and structural abnormalities of the kidneys have been found to run in families Among these are various infections of the kidneys known as nephritis, in which a susceptibility to the infection appears to be dominant.

Polycystic Kidney

A structural abnormality known as polycystic kidney, so called because of the presence of cavities in the kidney tissue, is frequently met with The condition causes insufficient functioning of the kidneys According to Gordon and Trasoff[1] it is found in one case in 500 at postmortem examination. The authors state that the hereditary aspect of polycystic kidney has often been noted, and a familial history is of the greatest diagnostic importance In a family studied by them a father who died of chronic nephritis had seven children, five with proven polycystic kidney disease. A brother of this father and one of the brother's daughters also had polycystic kidney disease This pedigree suggests a dominant gene Congenital cystic kidney leading to death soon after birth is said to be recessive.

ENDOCRINE GLANDS

Reference has already been made to the part played by the endocrine glands in such conditions as gigantism, dwarfism, hair growth, etc It is probable that these glands are concerned as links in the chain of development of many other hereditary differences, although in only a few cases do we have the evidence to establish the connection In the cases mentioned below, genes are known to control the functioning of endocrine glands.

Diabetes Mellitus (Sugar Diabetes)

This serious form of diabetes is caused by a failure of the endocrine cells in the pancreas to secrete an adequate amount of the hormone insulin, which is necessary for the metabolism of sugar in the body Excess sugar therefore accumulates in the blood and is excreted by the kidneys There are severe symptoms, including loss of weight and strength, excessive thirst, and overactivity of the kidneys, leading eventually to coma and death unless insulin is supplied from an external source.

Environmental factors such as syphilis, poisons, and overweight are important in favoring the development of diabetes mellitus in those who

[1] G R. Gordon and Abraham Trasoff, Congenital Polycystic Kidney, with Report of Its Occurrence in Several Members of One Family, *Am. J. Med. Sci*, 194:112-117, 1937.

are susceptible. Sex is also a factor: the disease is more common in women than in men Racial background is also a factor.

There have been many investigations and long discussions as to its mode of inheritance In a recent thorough study, Steinberg and Wilder[1] analyzed the data gathered at the Mayo Clinic over a two-year period by interviewing 1,981 consecutive patients who had the diagnosis of diabetes mellitus entered on their record for the first time during the current visit The authors conclude that only the hypothesis of a simple recessive gene can explain their data They state that about 1 per cent of the population of the United States have been diagnosed as diabetic. Naturally, not all who show symptoms have been discovered. Another 4 per cent are thought to carry the genes making them susceptible, and the fact that some of these do not develop the disease is due to favorable environmental or genetic factors

Diabetes may affect children and adults of any age, with the average age of onset in the late forties and the most dangerous period in the fifties

If we accept 5 per cent as the frequency of the double-recessive genotype in the population, as suggested by Steinberg and Wilder, the expected frequency of the gene is $\sqrt{5}$, or about 22 per cent.

In some families, however, diabetes mellitus seems to follow a dominant pattern of inheritance As with certain other human traits, it is possible that several distinct genetic types exist

Diabetes Insipidus

Diabetes insipidus has been defined as "a rare chronic condition characterized by an increased thirst and the passage of large quantities of urine of low specific gravity It is due to a deficiency of pitressin, a hormone produced by the posterior lobe of the pituitary gland which regulates the water metabolism of the body, or to an irresponsiveness of the kidney to this hormone."[2] There is no sugar or albumin in the urine, and the disease usually does not seem to have any deleterious effect on the general health or length of life It is an inconvenience in that it necessitates the frequent drinking of water and urination day and night. The amount of water ingested and eliminated varies greatly, ranging from 4 to 35 quarts daily. The restriction of fluids is said to cause headache, muscular pains, fatigue, abnormally low temperature, and rapid pulse The trouble usually appears in infancy or childhood and persists throughout life. In infants it may cause serious injury or death, if unrecognized

[1] G. Steinberg and R M Wilder, A Study of the Genetics of Diabetes Mellitus, *Am. J. Human Genet*, 4:113-130, 1952.

[2] C. B. Pender and F C. Fraser, Dominant Inheritance of Diabetes Insipidus' A Family Study, *Pediatrics*, 2:246-251, 1953.

Under living conditions where water is scarce, as in the desert, it might be dangerous to the individual

Most cases are inherited as a typical dominant, and in these the symptoms respond to the treatment with pitressin This hormone is necessary for the reabsorption of water in the kidney tubules Pender and Fraser studied a large pedigree covering six generations, including 40 individuals who were probable victims of the disease As required by theory, every affected individual had an affected parent, and approximately half of the offspring of affected parents were affected These investigators regard another type of diabetes insipidus, in which there is an actual defect of the kidney tubules, as a sex-linked recessive This type is not affected by pitressin

DIGESTIVE SYSTEM

Comparatively few hereditary differences have been reported for the digestive system, and in some of these the exact mechanism is still in doubt

Constricted Stomach (Pyloric Stenosis)

This condition, which appears in infancy, is characterized by violent vomiting There is an abnormal contraction of the lower, or pyloric, end of the stomach, which prevents the normal exit of food from the stomach If not properly treated, most affected persons die as infants One pedigree has been reported in which a father and his son and daughter were afflicted.[1] There seems to be evidence that it is inherited as a recessive The concordance in one-egg twins is very high Penetrance seems to be nearly complete in males, but much reduced in females Surgery is said to be an effective cure in most cases

Ulcers

One factor in the development of ulcers of the stomach and duodenum seems to be an excessive secretion of hydrochloric acid This causes the self-digestion of an area of the stomach (usually in the pyloric region) or in the intestinal wall, resulting in the production of raw ulcers. The ulcers are often difficult to heal and may become dangerous, either by reason of the loss of blood they occasion or because of infections following the perforation of the wall of the affected organ The activity of the nervous system seems to be a factor in the excessive secretion of hydrochloric acid by the stomach.

In a clinical study in the United States, the evidence indicated that predisposition to peptic ulcer is hereditary, probably as a simple reces-

[1] E. J. Caulfield, Familial Incidence of Pyloric Stenosis, *Am. J. Diseases Children*, 32:706–708, 1926

sive.[1] The author compared the families of 255 ulcer patients with the families of 400 patients having other diseases, finding that stomach ulcers were almost five times as frequent in the former group as in the latter. In this study the *family* was taken to indicate parents, brothers, and sisters of the patient. From the frequency of ulcers in the 255 families it was concluded that only about one-half of the persons genetically susceptible actually developed the disease Apparently, environmental factors necessary for the production of the symptoms were lacking in about 50 per cent of the cases

A study in England[2] led to the conclusion that hereditary factors are of importance in determining the development of peptic ulcer The authors found a strong tendency for sibs to develop ulcers in the same site.

REPRODUCTIVE SYSTEM

The reproductive system in man is subject to numerous individual variations as well as abnormalities, some of which have been shown to be hereditary. The tracing of family histories involving the reproductive system is difficult because the system is different in the two sexes, and the natural tendency is toward concealment of any peculiarity. The case of female intersexuality, or pseudohermaphroditism, appears to rest in part upon a hereditary basis This was referred to in Chap. 9 The tendency to produce twins likewise runs in families. The hereditary basis of twinning was considered in Chap 9

Hypospadias

Hypospadias is a developmental abnormality of the penis in which the opening of the urethra is on the undersurface rather than at the end of the penis The defect results from a failure of the groove, which represents the urethra at one stage in embryonic development, to close over normally and form a tube According to Dr. Lenz, about one male in three hundred shows this malformation to a greater or less extent. In certain families it has been traced through the male line for several generations, behaving as a dominant. It tends to be irregular in its expression, and many sporadic cases occur

CANCERS AND OTHER MALIGNANT TUMORS

The word *cancer* is derived from the Latin word for crab and refers to any persisting and destructive (malignant) growth derived from the

[1] Julius Bauer, The Relation between Peptic Ulcer and Cancer of the Stomach from the Genetic Point of View, *Rev Gastroenterol*, 7:21-24, 1949.

[2] R Doll and J. Buch, Hereditary Factors in Peptic Ulcer, *Ann. Eugenics*, 15:135-146, 1950.

individual's own cells The epithelial tissues include the outer skin, the mucous membranes, which line cavities, and glands which develop as ingrowths of the skin or mucous membranes In medical literature a cancer arising from epithelial tissue is known as a carcinoma Most malignant tumors of middle age and advanced years are of this type, less often such tumors develop from cells of other tissues such as bone, cartilage, connective tissue, muscle, and nerve cells When a malignant tumor develops from nonepithelial cells, usually connective-tissue cells, it is known as a sarcoma Most cancers in persons under 24 are of this type

Malignant tumors are distinguished from nonmalignant growths such as moles, warts, etc , by the fact that the latter grow for a time and then spontaneously cease growth, while malignant tumors keep on growing until eventually they invade the surrounding areas, causing the destruction of normal tissues and organs and finally death Malignant growths have a strong tendency to release abnormal cells into the blood vessels or lymph channels to be carried over the body and set up secondary malignant growths This transfer from a primary focus to a distant one is known as metastasis A cancer expert is able to diagnose a cancer prior to the invasive and destructive phases by microscopical examination of the cells In cancer the cells show abnormal nuclei and atypical mitotic figures

The factors contributing to the origin of malignant tumors are not yet fully known, but it is certain that in many cases there are two sets of factors. (1) the natural susceptibility of the individual and (2) some inciting environmental agent It is well established that persons differ in their natural susceptibility to cancer and that these differences are hereditary. It is probable, however, that cancer of some kind would develop in almost everyone under the appropriate stimulus Repeated exposure of the skin to X rays and radium frequently causes skin cancer, and in the early days before this danger was recognized and guarded against, many doctors and X-ray workers fell victims to it In some industries such as clock and watch factories numerous workers in radium developed sarcoma of the bones as a result of chronic radium poisoning Tar, soot, lubricating oils, and various products of coal tar in contact with the skin have a similar effect. It is reported that in certain chemical industries a majority of the workers who are repeatedly exposed to poisons such as aniline develop cancer of the bladder There is good statistical evidence that heavy smoking of cigarettes over a period of many years is an important factor in cancer of the lung The list of carcinogenic environmental agents could be greatly extended.

The precise manner in which such irritating agents convert a normal healthy cell into a malignant cell is not known. It was suggested as early as 1914 by the famous biologist Theodor Boveri that malignancy results from a change in the chromosome constitution of the cell, of such a na-

ture as to lead to uncontrolled multiplication of its descendants. The aberrant behavior of cancer cells makes the mutation theory an attractive one, but the proof that the changes in the cells are nuclear rather than cytoplasmic is still lacking Indirect evidence that cancer may in some cases be due to somatic mutation is the fact that numerous carcinogenic agents also induce mutations Among these are X rays, radium, ultraviolet rays, and certain organic chemicals.

Malignant tumors affect all of the systems and organs of the human body, although some parts are much more frequently affected than others. The study of family pedigrees shows that cancers of specific types run in families, in many of these there is no doubt that heredity is an important factor The examples discussed below belong to this category

Cancer of the Breast

Numerous investigations in this country and in Europe show that breast cancer tends to run in families. These studies are cited in a report from the Laboratory of Human Genetics, University of Utah[1] Gardner and Stephens studied a Utah kindred, including 668 individuals. Nine cases of breast cancer and four cases of breast tumor, three of which were probably cancerous, were found in four generations. The authors state that this is a frequency about twenty times that in the general population in Utah over the age of thirty Of females dying in Utah in 1946 about one in 40 died of breast cancer. In this kindred one-half of the deaths of mature females were due to breast cancer, and some of those who died from other causes had breast cancer or breast tumor at the time of death

The period of onset, duration of the disease, and clinical history are reported to be similar among the members of a family. The authors conclude that heredity is a predisposing factor for breast cancer, but they offer no suggestion as to the mode of inheritance. They are continuing their studies in the hope of solving this problem. They, as well as others, emphasize the importance of frequent examinations for the early detection and treatment of breast cancer in families where the disease has occurred previously.

Xeroderma Pigmentosum

This hereditary abnormality is often discussed in works on diseases of the skin, the name meaning pigmented dry skin. At birth, the skin is apparently normal. According to Cockayne, the first symptom, an abnor-

[1] E. J. Gardner and F E. Stephens, Breast Cancer in One Family Group, *Am. J. Human Genet.*, 2:30–40, 1950

mal avoidance of light, may be noticed during the first few weeks of life Reddening of the exposed skin of the face and hands, and of the whites of the eyes, follows in succeeding months, usually before the third year Freckles, which may even appear on the lips and whites of the eyes, accompany or closely follow the reddening The freckles grow larger, more numerous, and darker. Between the freckles are white areas which undergo degenerative changes, leading in most cases to the development of cancerous growths

There is no known cure, and death ordinarily results between ages 5 and 15 years, although in rare cases where the disease appears later and progresses more slowly, life may be prolonged to the age of 40 Fortunately the disease is rare; only a few hundred cases have been reported

Xeroderma pigmentosum is a striking example of an inherited condition which requires for its expression the cooperation of a gene with an environmental factor—in this case light Cockayne states.

> The distribution of the pigmentation and other lesions corresponds closely with the parts exposed to sunlight, the face and backs of the hands suffer most the neck, the upper part of the chest, the forearms and dorsal surfaces of the feet are less severely affected, and only if the children have been allowed to go out with bare legs does the skin of the legs become greatly altered Lesions on the covered parts are relatively uncommon and usually trifling

In some families brothers and sisters of children who have the disease are heavily freckled, but are otherwise normal It has been suggested that this type of freckling (which, unlike ordinary freckles, shows no correlation with red hair) indicates a person who is heterozygous for the gene of xeroderma pigmentosum. If this is true, the marriage of two such persons will stand a chance of one in four of producing afflicted children, since the numerous pedigrees clearly show that the disease is recessive

Von Recklinghausen's Disease (Neurofibromatosis)

This particular type of tumor is usually inherited as a dominant, although in a few families some other explanation seems necessary Cockayne gives a lengthy discussion of the disease with numerous pedigrees

The most common lesions are large pigmented spots in the skin, with multiple tumors of the skin and peripheral nerves. Less often the brain, spinal cord, and sympathetic nervous system become tumorous. The pigmented spots may be present at birth, but the tumors usually do not appear until puberty or later The tumors frequently develop into cancers and cause death

Other abnormalities such as mental deficiency and defects of the reproductive system often accompany the tumors.

Cancer of the Digestive Tract

Cancer of the digestive tract ranks first among fatal cancers. A statistical study[1] of cancer in Cook County, Illinois (which includes Chicago), with a population at the time of about 4 million, showed that 5,480 deaths from cancer were reported among residents of the county. Of these, cancer of the digestive tract accounted for 54.7 per cent in males and 42.3 per cent in females Among the reasons for the high fatality in cancers of the digestive tract is the frequent delay in the discovery of internal cancers

Cancer of the stomach stands first as a cause of death from cancer in men and third in women Its tendency to afflict certain families has long been noted.

Cancers of the intestines, rectum, and anus taken together kill nearly as many persons as cancer of the stomach. Cancer of the small intestine is rare Cancer of the large intestine (colon and rectum) is frequent. A number of investigations have shown that cancer of the colon commonly develops from benign tumors known as polyps, growing on the lining of the intestine There is good evidence from pedigree studies that the tendency to develop these polyps is inherited as a dominant. A recent investigation of a family group of 45 individuals in Utah by Gardner and Stephens[2] disclosed nine cases of cancer of the large intestine The distribution of the cancers in this family confirmed the theory of dominant inheritance of intestinal polyps as a predisposing factor for cancer.

Dr. Dukes,[3] Director of Research Laboratory, St Mark's Hospital, London, has published a thorough study of 41 polyposis families. His results, based upon many years of research, are in agreement with those of Gardner and Stephens. He finds that age of onset of symptoms is about 20 years, rarely before 10 or after 40, and that cancer is most likely to develop about 15 years after the onset of symptoms of polyposis.

Among the 753 members in his 41 families the number of cases of polyposis recorded so far has been 156 (77 males and 79 females). Of these, 114 subsequently developed cancer of the rectum or colon (55 males and 59 females). The appearance of the polyposis is shown in Fig. 128, and a typical pedigree in Fig 129.

Periodical examination by the physician of members of such families and surgical removal of polyps, or in extreme cases removal of the colon, is recommended. Dr. Dukes states that surgical treatment has prolonged

[1] H. F. Dorn, The Incidence of Cancer in Cook County, Illinois, 1937, *U.S Public Health Repts*, *Reprint* 2152, 55:628–650, 1940

[2] E. J. Gardner and F. E. Stephens, Cancer of the Lower Digestive Tract in One Family Group, *Am. J. Human Genet*, 2:41–48, 1950

[3] C. E. Dukes, Familial Intestinal Polyposis, *Ann Eugenics*, 17:1–29, 1952

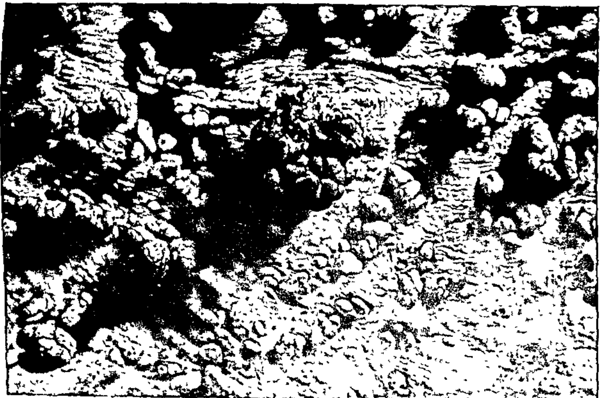


Figure 128. Surface view of mucous membrane of colon in familial intestinal polyposis. Approximately natural size. (*From Dukes, Ann Eugenics, vol.* 17, *no* 1, *plate* I, 1952)

the lives of many patients who would otherwise have died of cancer, and the general health of patients operated on in the premalignant phase has been improved by treatment

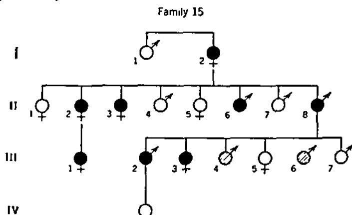


Figure 129. Pedigree of polyposis and cancer of the rectum or colon Blackened symbols, cancer; diagonally lined symbols, polyposis, open symbols, unaffected. (*From Dukes, Ann Eugenics*, **17**:16, 1952)

Cancer of the Eye (Retinoblastoma)

This is a rare type of malignant tumor that develops in the eyes of infants and children up to about four years of age The disease is almost always fatal unless irradiation or surgery is applied before the cancer has spread beyond the eyeball Either one eye, or both, may be affected In a recent comprehensive survey by Falls and Neel[1] in Michigan the frequency of the disease was estimated at about one in each 20,288 live births, covering the period between 1938 and 1947.

There have been numerous cases reported in which an affected person has had a cancerous eye removed as a child and later has produced one or more children who developed the same disease. This fact as well as other evidence indicates that the disease depends upon a dominant gene Most affected children, however, do not have an affected parent or other affected relative. In such cases the presence of the disease has been explained as due to new mutations or to lack of complete penetrance of the gene—for some unknown reason the gene may have failed to express itself in the parent.

Falls and Neel state that persons surviving bilateral retinoblastoma, and who as a result are blind, seldom have children, while those who survive the unilateral disease reproduce at about the normal rate. They find that from 8.5 per cent to 21.7 per cent of reported cases are bilateral

[1] H F. Falls and J V Neel, Genetics of Retinoblastoma, *Am. Med. Assoc Arch Ophthalmol.*, **46**:367–389, 1951.

They estimate the rate of mutation to the defective gene at 2 3 per 100,000 and calculate that as a result there is a slow increase of the frequency of the disease in the population It is interesting to note that if no one who had the disease produced children, the frequency of the disease would remain at double the mutation rate (the net rate of mutation to the abnormal gene per chromosome per generation), provided it is due to a dominant autosomal gene

NERVOUS SYSTEM

In man the nervous system reaches a superlative degree of complexity. Its functions are intricate and diverse, ranging from the detection of all manner of stimuli and the regulation of muscular and glandular activities to the highest mental processes of the brain The great development of that part of the brain concerned with conscious and voluntary activities (cerebrum) constitutes man's chief claim to superiority over all other forms of life.

Among individuals who are regarded as normal, the nervous system shows great variability, and the normal grades downward by imperceptible stages into the abnormal Included in the latter category we find a long list of variations consisting of defects and diseases of many sorts Some of these exhibit marked physical signs and symptoms Others are detectable at present only from the abnormal behavior of affected individuals, although undoubtedly they rest on physical changes in the nervous system, in the glands of internal secretion, or in other parts of the body.

Let us first consider an example of a normal hereditary difference which apparently has no adaptive significance This will be followed by a description of a few of the best-known hereditary defects and diseases of the nervous system Afterward will come a brief discussion of the inheritance of special talents For further details and additional examples the reader is referred to the books and articles cited in the following pages

Tasters and Nontasters

In 1931 A. L Fox,[1] an American chemist, accidentally discovered that persons differ in a striking way in their ability to taste a synthetic chemical compound known as phenylthiocarbamide ($C_7H_8N_2S$). Most persons find that crystals of the substance placed on the tongue give a very bitter taste, while other persons get no taste Fox also found that his experimental subjects reacted in the same way to numerous other thiocarbamides.

[1] A. L Fox, The Relationship between Chemical Composition and Taste, *Proc. Nat Acad. Sci U S*, 18:115–120, 1932

Following up Fox's discovery, L. H. Snyder[1] concluded from his studies of parents and children in 100 families that the taste deficiency was inherited as a single recessive. A. F. Blakeslee and M. R. Salmon[2] in 1931 independently reached the same conclusion. This rule seems to hold in most cases, but some exceptions have been found which have not been explained. Blakeslee and Salmon found great variability in the acuity of taste for phenylthiocarbamide among the tasters, ranging from a sensitivity for solutions of 1:500,000 to those of 1:5,000, with the commonest threshold (lowest concentration at which the substance can be detected) at about 1:80,000. They also found that persons classed as nontasters, based on their inability to taste the crystals, could detect a bitter taste in strong solutions of the substance, although some required a warm saturated solution. Nontasters, like tasters, vary about their own most common threshold. When the results of tests are plotted, it turns out that there is a slight overlap of the curves of variability of threshold for the tasters and the nontasters provided fair numbers are obtained. This is well illustrated in a study in England by N. A. Barnicot[3] (Fig. 130). It is concluded that the double dose of recessive gene of the nontaster raises the threshold for this group of substances to a very high level, while the dominant gene of the taster conditions a low threshold. Other factors, however, either genetic or environmental in nature, cooperate to fix the precise threshold. Among these other factors are age, sex, and race. Sensitivity to phenylthiocarbamide seems to decrease with age, and females are slightly more sensitive than males (Harris and Kalmus).[4]

The differences in the frequency of the recessive gene among the major racial groups is well shown in Fig. 130, in spite of the fact that the numbers are small. Numerous studies by various investigators, tabulated by Barnicot and by Gates,[5] show that for Caucasoids about 70 per cent may be classed as tasters, and for African Negroids and Mongoloids about 95 per cent. Mixedbloods are naturally intermediate. The published figures show marked variations among the subgroups within each of the three major racial groups. A part of this variability is probably due to differences in technique employed by different investigators and to the difficulty of obtaining reliable results from some peoples in a test requiring a subjective response from the tested person. Harris and Kalmus

[1] L. H. Snyder, Inherited Taste Deficiency, *Science*, **74**:151–152, 1931.

[2] A. F. Blakeslee and T. N. Salmon, Genetics of Sensory Thresholds: Individual Taste Reactions for Different Substances, *Proc. Nat. Acad. Sci. U.S.*, **21**:84–90, 1935.

[3] N. A. Barnicot, Taste Deficiency for Phenylthiourea in African Negroes and Chinese, *Ann. Eugenics*, **15**:248–254, 1950.

[4] H. Harris and H. Kalmus, The Measurement of Taste Sensitivity to Phenylthiourea (P.T.C.), *Ann. Eugenics*, **15**:24–31, 1949.

[5] Reginald Ruggles Gates, "Human Genetics," The Macmillan Company, New York, 1946.

used a new technique which seems to overcome this last difficulty So far as known this trait is a good example of a gene difference with no adaptive value

The physiological basis for this hereditary taste difference is still unknown, but its existence is highly interesting and important because it

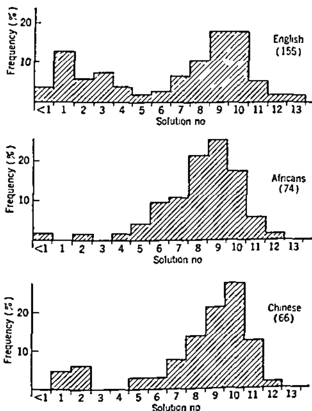


Figure 130. Taste thresholds for phenylthiourea in English males, African Negroes (71 males, 3 females), and Chinese (55 males, 11 females) Concentration in Solution 1, 1,300 mg. per liter, successively reduced 50 per cent at each step to 0 32 mg per liter in Solution 13. (*From Barnicot, Ann Eugenics,* **15**:252. 1950.)

demonstrates the possibility of human beings living in different sensory worlds We know of many other respects in which individuals differ in their sensory perceptions, including those of color, sound, and odors. It is highly probable that differences in taste—where taste is used in the figurative sense to denote a decided preference for one thing over another—may often depend upon physical differences in the nervous sys-

tem. The old saying that "regarding tastes there can be no argument" thus appears to rest upon a sound biological basis.

Deafness

Deafness may result either from environmental or hereditary causes Babies are sometimes born deaf as a result of infection with syphilis or rubella (German measles) acquired *in utero* from the mother. Children are frequently rendered deaf by infections such as meningitis, influenza, and scarlet fever Injuries sometimes cause deafness. Where deafness results from infection or injury it is not transmitted to the offspring

Many cases of congenital deafness and of deafness appearing in later life are hereditary *Hereditary congenital deafness* (due to imperfect development of the internal ear) has been studied extensively. There is evidence for two independent recessive mutations. Deafness develops if either recessive gene is present in the homozygous state. In most cases the deaf person has only one pair of these genes. If he should marry a deaf partner who has the other pair of recessives, the children should all have normal hearing They will, however, be heterozygous in both pairs and thus likely to produce deaf children if they marry persons who are heterozygous for either gene. Genetically, it is apparent that this case in man is like the sweet pea case described in Chap 6, where we found that white flowers owe their lack of pigment to either one of two distinct recessive mutations

Certain other types of hereditary deafness have their onset in middle age. Among these are *auditory nerve atrophy* and *otosclerosis* Atrophy of the auditory nerve begins at about 40 and may progress for several years until complete deafness results. It is apparently due to a dominant gene. Otosclerosis is a type of progressive deafness having its onset at about 30; the hearing gradually diminishes, but is not entirely lost It is usually accompanied by subjective buzzing or ringing in the ears The immediate cause is an abnormal growth of bone about the ear bones of the middle ear. In some families otosclerosis is inherited as a dominant.

Hereditary Muscular Atrophy

Under the above designation ten or more distinct diseases have been described In some, the muscles themselves seem to be primarily affected In others, the seat of the trouble is in the nervous system. Destruction of a cell body of a motor neuron in the brain or spinal cord, whether the result of a gene, a virus infection like infantile paralysis, or a wound, leads to a degeneration of its nerve fiber and the muscle cells supplied by the fiber. The different forms of muscular atrophy are distinguished in part by the various muscle groups affected.

Hereditary muscular atrophy usually involves a progressive wasting of the muscles, so that the afflicted person becomes steadily weaker until finally he is helpless During this process the muscles may appear to increase in size owing to the accumulation of fatty tissue The symptoms become evident at different ages, varying from early childhood to middle age according to the type of the disease Death may follow within a few years of the onset of the symptoms

In the severer types muscular atrophy shows recessive inheritance, but pedigrees of milder forms have frequently been published indicating dominance. A sex-linked recessive type known as *progressive muscular dystrophy* also has been described in two recent papers [1, 2] Males only are affected, and as very young children Death usually occurs before 20 None of the affected reproduce

Hereditary Ataxia

The first symptoms of this disease point to defective muscular control In the standing position the body sways, and with the eyes closed the victim is not able to stand at all The gait in walking resembles that of a drunken person In the advanced stages the patient loses completely the power of independent movement, becoming a helpless invalid The immediate cause of these symptoms is a degeneration of the sensory neurons in the spinal ganglia, with the consequent loss of sensations from the muscles. The spinal cord, as well as the brain, may also be affected

A recessive type of the disease known as *Friedreich's ataxia* is said to be comparatively common in certain valleys in Switzerland where much inbreeding has taken place

A milder form of ataxia in which the degeneration is centered in the brain as well as the cord, and which is inherited as a dominant, has been reported a number of times. One of the latest of these reports[3] is a study of a family of 343 members covering six generations, in which the disease appeared as a dominant in 45 members The average age of onset was 26 5 years. The age of death of affected persons averaged 39 6 years for men and 35 2 years for women In every case an affected person had an affected parent.

[1] F E Stephens and F. H. Tyler, Studies in Disorders of Muscle V The Inheritance of Childhood Progressive Muscular Dystrophy in 33 Kindreds, *Am J. Human Genet*, 3:111-125, 1951.

[2] A C. Stephenson, Muscular Dystrophy in Northern Ireland 1 An Account of the Condition in Fifty-one Families, *Ann. Eugenics*, 18:50-93, 1953

[3] J. W. Schut, Hereditary Ataxia, a Survey of Certain Clinical, Pathologic, and Genetic Features with Linkage Data on Five Additional Hereditary Factors, *Am. J. Human Genet*, 3:93-110, 1951.

Paralysis Agitans (Parkinson's Disease)

In 1817, James Parkinson wrote "An Essay on the Shaking Palsy," in which he described the symptoms of paralysis agitans as follows: "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellect being uninjured." The symptoms vary greatly in severity among individuals, and in the same person fluctuate with the emotional state, tending to be exaggerated under stimuli that cause excitement. Affected persons may be of a naturally superior physical and mental capacity. The milder forms of the disease seem not to interfere seriously with performance of mental work. That part of the brain known as the extrapyramidal system is the seat of the disease.

Numerous studies of paralysis agitans were published during the nineteenth century. Since 1900 there have been several investigations of its genetic aspects. Dominant heredity has been suggested. This explanation is confirmed from Sweden in a thorough study based upon the clinical analysis of 262 cases.[1] Care was taken to exclude persons with tremors due to arteriosclerosis and chronic encephalitis. Mjönes estimates the incidence of paralysis agitans in Sweden at about 1.6 per thousand among individuals of 50 or over. He found that the age of onset varied between 7 and 81 years, with 52 as the average. The symptoms varied greatly. Tremor was the most constant and in some cases the only symptom. Mjönes' genetic analysis, based upon the study of pedigree charts, strongly indicated dominant heredity, with lack of complete penetrance: only about 60 per cent of persons carrying the gene developed the disease. The factors that prevent the expression of the gene in the remaining 40 per cent are unknown.

Epilepsy

Epilepsy (*epilepsia*, a seizure) is defined in "Blakiston's New Gould Medical Dictionary" as follows:

> A disorder of the central nervous system, characterized by explosive nerve cell discharges and manifested by transient episodes of unconsciousness or psychic dysfunction, with or without convulsive movements. The discharge or seizure is associated with a pronounced change in the electric activity of the brain cells, and the normal synchrony is disturbed by a dysrhythmia.

Several types, based upon particular complexes of symptoms, have been described; some are accompanied by lesions in the brain or by

[1] Henry Mjönes, Paralysis Agitans: A Clinical and Genetic Study, *Acta Psychiat. et Neurol.*, suppl. 54, 1949.

metabolic disorders; in other types there is no apparent brain damage. Environmental and genetic factors are both important in epilepsy Injuries and tumors may lead to epilepsy. Where no specific lesion or brain

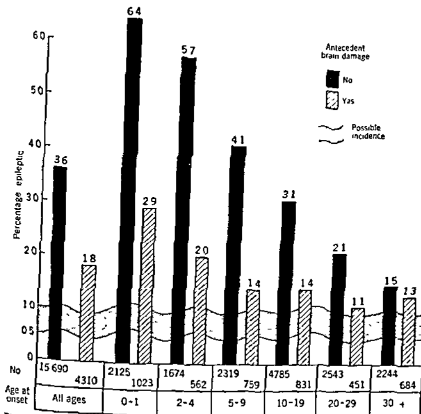


Figure 131. Incidence of epilepsy among 20,000 near relatives of epileptics with reference to antecedent brain damage and age at onset of the seizures The black bars indicate patients without antecedent brain damage, and the hatched bars those with evidence of such damage The stippled band near the bottom represents draftees rejected (0 515 per cent) because of epilepsy during the First World War. The waviness and spread of the band suggest the possible inaccuracy of this figure (*From Lennox, J. Am Med. Assoc*, *vol.* 146, 1951.)

disease and no environmental factor can be blamed, the epilepsy is known as *essential*, or *idiopathic* (*idios*, one's own), or *metabolic* epilepsy. In this type there is good evidence for heredity as a factor

Dr. Lennox,[1] of Harvard Medical School and the Neurological Institute of the Children's Medical Center, in Boston, and his colleagues have

[1] W. G Lennox, The Heredity of Epilepsy as Told by Relatives and Twins, *J Am. Med. Assoc*, 146:529–536, 1951.

studied the family histories of more than 4,000 epilepsy patients and their 20,000 near relatives The results show that near relatives of epileptics are several times as likely to have the disease as are persons in the general population (Fig 131) The difference between the relatives of patients and the general population in frequency of epilepsy is not nearly so great where the patient shows brain damage before the onset of seizures, some of these cases are due to environmental factors.

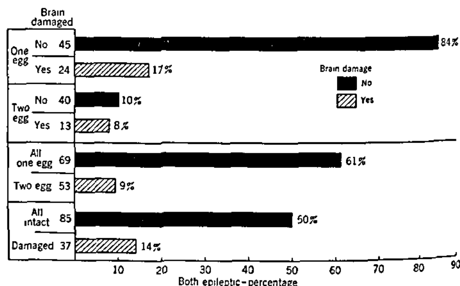


Figure 132. Percentage of twin pairs in which both co-twins have a history of seizures. Black bars represent twins without evidence of brain damage prior to the onset of seizures, and hatched bars those with such evidence. (*From Lennox, J. Am Med Assoc., vol* 146, 1951)

The comparison of identical and fraternal twins is in agreement with the study of relatives of epileptics (Fig 132) Concordance is very high among one-egg twins—about eight times that among two-egg twins in cases without evidence of prior brain damage. Not only are both members of a pair of identical twins likely to be affected if one is affected, but the types of seizures also are much more likely to be the same than with two-egg twins.

In a later study[1] Lennox has expanded his studies to include 173 twin pairs subject to seizures. The results confirm those of the first 122 pairs He finds that the degree of concordance in dizygotic twins points to a

[1] W. G. Lennox and D H. Jolly, Seizures, Brain Waves and Intelligence Tests of Epileptic Twins, *Proc. Assoc Research Nervous Mental Diseases*, 1953, in Davenport Hooker and Clarence C. Hare (eds), "Genetics and the Inheritance of Integrated Neurological and Psychiatric Patterns," The Williams & Wilkins Company, Baltimore, 1954.

simple recessive, but he does not rule out alternative genetic hypotheses Penrose[1] found 6 patients among 210 idiopathic epileptics whose parents were first cousins, a proportion high enough to make him suspect recessive determination. In a trait of rather high frequency, like epilepsy, one does not expect a great increase in percentage of consanguinity among the parents of affected children

In 1929 Berger in Germany discovered that the brain of a normal person at rest produces rhythmical electrical discharges With a measuring instrument known as an electroencephalograph, the discharges can be recorded on paper as wavy lines (Fig 133) In about 90 per cent of idiopathic epilepsy the rhythm of the brain waves is abnormal Lennox and his coworkers find that concordance among identical twins is 61 per cent for all abnormalities compared to 7 per cent among fraternal twins He concludes that the striking likeness of brain-wave abnormalities in persons with the same heredity adds weight to the suggestion that brain-wave dysrhythmia may be the observable expression of the predisposition to seizures

From his twin studies Lennox finds that in the absence of brain damage epilepsy does not affect mentality adversely Where there is evidence of brain damage, however, the IQ of the affected twin is distinctly lower Penrose also finds little evidence that epilepsy in itself tends to cause intellectual deterioration. Epilepsy is not inconsistent with great creative ability. Among famous persons who have suffered from epilepsy are the novelist Dostoievsky and the painter Van Gogh As pointed out by Penrose, some form of epileptic seizure is highly characteristic of mental defectives. Neither of these conditions, however, is the cause of the other, both are the result of a common cause

Convulsive seizures are found in other species of mammals also: certain strains of inbred mice are highly susceptible to seizures upon stimulation with loud sounds, in Viennese white rabbits spontaneous convulsions depend upon a recessive gene

Huntington's Chorea

This is one form of St. Vitus's dance, a classical description of which was given by Huntington, of Ohio, in 1872 According to Penrose,[2] citing Critchley, the disease was probably derived from English immigrants, and in earlier times their affected ancestors and collaterals suffered penalties for supposed witchcraft. It develops usually during the thirties or forties, although not infrequently at earlier or later ages The early symp-

[1] L. S. Penrose, (Colchester Survey), A Clinical and Genetic Study of 1280 Cases of Mental Defect, Med Research Council (Brit) Spec Rept Ser, No 229, 1938

[2] Lionel S Penrose, "The Biology of Mental Defect," Grune & Stratton, Inc, New York, 1949.

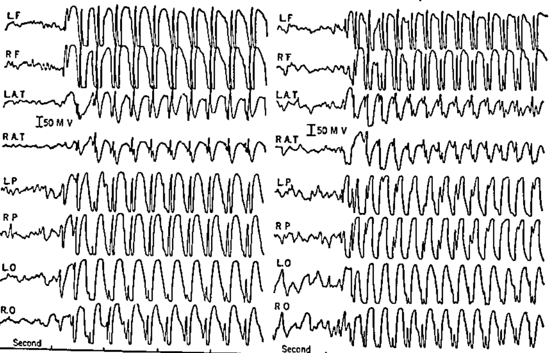


Figure 133. Electroencephalographic tracings of a pair of identical twins, aged 11, at the outset of a petit absence. The letters indicate placement of electrodes, namely, left and right frontal, left and right anterior temporal, left and right parietal, and left and right occipital leads Reference leads were on the ears. These samples illustrate the likeness of seizure pattern, even in some of the finer details, such as the tendency of spikes in the anterior temporal leads to surmount the waves and the relatively short spikes in the occipital leads. In the parietal leads, however, the placement of spikes is different. (*From Lennox, J. Am. Med. Assoc., vol.* 146, 1951.)

tom is persistent twitching of the head, limbs, and trunk, which tends to grow worse as time passes; mental deterioration commonly, but not always, ensues The physical changes in the nervous system are brain atrophy with disappearance of nerve cells in the cerebrum

Many pedigrees have been collected in this country and in Europe which clearly show that it is inherited as a single dominant, the gene passing from heterozygous parent to half of the children There is no known preventive or cure Owing to the seriousness of the disease and the wide variability in age of onset, not only patients afflicted with the disease but also their seemingly healthy brothers, sisters, and children might well forego having children Unfortunately there seems to be no reliable way of identifying heterozygotes until symptoms develop

Feeblemindedness (Mental Deficiency)

Feeblemindedness is a condition of abnormally low intellectual capacity existing from birth or an early age, caused by abnormal development of the brain or destruction or degeneration of brain cells It is not a single biological entity There are many degrees of feeblemindedness ranging from idiocy, in which the mental capacity is so low that the afflicted individual may not even be able to dress or feed himself, through stages of increasing capacity, finally shading imperceptibly into low-grade normal mentality

The range of variability in mental capacity is much greater than the range for physical differences such as height, head form, and weight Based upon the scores made in standardized "intelligence" tests, it is found that the population in general varies in accordance with the normal probability curve. By definition, an intelligence quotient (IQ)[1] of 100 is the mean. About 50 per cent of the population have IQ's between 90 and 110, with about 25 per cent below 90, and 25 per cent above 110 A very few superior individuals attain an IQ of 180 or higher

Individuals in the lower ranges of intelligence are subdivided as follows

80–90	Dull normal
70–80	Borderline
50–70	Morons
20–50	Imbeciles
Below 20	Idiots

In the United States those with an IQ below 70 are classed as feebleminded; in the British Islands, as mentally defective

The intelligence score is based upon an average of several abilities in

[1] The IQ is found by dividing the mental age, as indicated by standard tests, by the chronological age and multiplying by 100. For example, if a child has a mental age of ten and a chronological age of eight, his IQ is $\frac{10}{8} \times 100 = 125$

which the individual may show uneven development, while certain special abilities such as musical, artistic, and mechanical ability are not tested at all. A low IQ sometimes accompanies high proficiency along one of these special lines

There is no general agreement as to what is meant by intelligence. The so-called intelligence tests have usually aimed to test innate mental capacity rather than the knowledge acquired by experience, but it is recognized that no test yet devised eliminates the latter factor. Moreover, it is



Figure 134. Recessive microcephaly in a male idiot, aged 32 Note the small skull cap, with face, neck, and shoulders of normal size Head measurements· length 154 mm., breadth 117 mm , height 106 mm , cephalic index 0.76 Product of a marriage of first cousins, the pedigree is shown in Fig. 135. *(From Penrose, "The Biology of Mental Defect," Grune & Stratton, Inc.)*

an obvious fact that intelligence as measured by the ordinary tests is not a single unit, but that many separate abilities exist. The present task of psychologists, in which a good beginning has been made, is to analyze intelligence into these special abilities and to devise means of measuring each by itself. After this is done it may be possible to show how these separate abilities are inherited. If we may judge from what we know of the inheritance of physical characteristics, we may anticipate a certain amount of independence among the mental abilities respecting mode of inheritance.

Microcephaly. The lowest grades of the feebleminded are usually abnormal physically The "true microcephalics," or "pinheads" (Fig 134), constitute a distinctive type. The following brief description is based on Penrose's book.[1] The microcephalic's head is relatively long, with reced-

[1] Penrose, *op. cit.*

ing forehead and inwardly sloping sides The low vertex is emphasized by the large ears and relatively normal face The brain is very small, sometimes weighing less than 1,000 g, in contrast to a normal weight of about 1,350 g. Post-mortem examination shows a much simplified pattern of the cortical convolutions; there may be no pathological lesions

The cause of the small head seems to be an arrest in the growth of the brain, with resulting premature closing of the sutures of the bones of the cranium, rather than the premature closing of the sutures as the primary factor. Penrose concludes that "If an anthropologist should find a skeleton of a microcephalic, he might well conclude that it had belonged to a

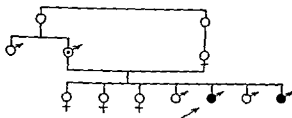


Figure 135. Pedigree showing microcephalic idiocy (*blackened symbols*) in two males in a family of seven The parents are first cousins The father of the microcephalics suffered from paranoid psychosis at the age of 41. The arrow indicates the microcephalic shown in Fig. 131. (*Courtesy of Lionel S. Penrose.*)

different species from *Homo sapiens* though closely related. It is remarkable that a single gene can produce such a gross change, compatible with life if not with fertility."

The rest of the body, though dwarfed, is often well developed, with relatively normal musculature and sexual organs. Microcephalics are usually active and fairly healthy. If well treated they are said to be among the happiest and most harmless of patients Those in institutions are usually of low imbecile grade

Numerous pedigrees have been published, indicating recessive inheritance. The parents are usually normal, and, as in the pedigree from Penrose (Fig. 135), often first cousins.

Environmental Feeblemindedness. Although the majority of feebleminded individuals probably owe their misfortune to heredity, congenital syphilis or infection *in utero* with the protozoan *Toxoplasma* or the viruses of rubella or equine encephalomyelitis are occasionally to blame. Other environmental factors, such as birth injuries and various postnatal infections, may be the cause. In a given case it may be difficult or impossible to determine the roles of hereditary and environmental factors

Amaurotic Idiocy

Amaurotic idiocy (*amaurosis*, blindness), of which several types have been described, is characterized by a progressive degeneration of the central nervous system It differs markedly from other types of idiocy. The disease is hereditary, and there is no known preventive or cure. The two most common types are designated as infantile and juvenile, respectively, in accordance with the age of the patients.

In *infantile amaurotic idiocy*, according to Rosanoff, the following symptoms are characteristic. The subjects seem normal and healthy at birth, but at ages between four and eight months the disease becomes manifest. The course is steadily progressive, and death usually ensues before the end of the second year of life. There is early impairment of vision, soon leading to blindness; a rapidly growing general muscular weakness; frequently epileptiform convulsions; and gradual emaciation. Post-mortem findings consist in very widespread and highly characteristic changes in the nerve-cell bodies throughout the central nervous system, including the spinal-root ganglia Individual cells are distended with fatty substance.

The disease is inherited as a single recessive. A large percentage of the cases arise from the intermarriage of relatives.

In *juvenile amaurotic idiocy* the child is normal until five to eight years of age. The early symptoms are a steady and rapid loss of vision, with loss of facial expression At the end of a year or two the patient is able merely to distinguish intensities of light or to count objects at close range. A fairly rapid mental deterioration, accompanied by marked speech disturbances, sets in, along with loss of vision. Later, progressive motor disturbances of posture and gait appear Epileptic seizures are characteristic of intermediate stages There is finally extreme emaciation with almost complete obliteration of mentality. Death usually occurs between the ages of 14 and 22 years.

The pathological changes in the nerve cells parallel those in the infantile type; nevertheless the two diseases are considered as genetically distinct The juvenile type is also inherited as a recessive. Cousin marriages are frequent among the parents of patients.

Schizophrenia (Dementia Praecox)

Schizophrenia (*schizo*, divided, *phrenia*, mind) is a term originated by a German, E. Bleuler, to replace the older name, dementia praecox, used to designate a certain type of mental disease which is said to affect from 0.5 per cent to 1 per cent of the population and to account for more than one-half of all patients in mental hospitals and more than a quarter of all patients in all hospitals in the United States. Bleuler's reason for suggest-

ing the change in name is set forth in the following quotation from an English translation of a book by Bleuler, as reported by Rosanoff

As the disease needs not progress as far as dementia and does not always appear praecociter, i e, during puberty or soon after, I prefer the name *schizophrenia*. . . . This disease may come to a standstill at every stage and many of its symptoms may clear up very much or altogether, but if it progresses, it leads to a dementia of a definite character It is characterized by a specific kind of alteration of thinking and feeling, and of the relations with the outer world that occur nowhere else

Lenz describes the disease and its symptoms in the following quoted paragraphs

The trouble usually begins in the second or third decade of life, but sometimes later. There are various forms of the disorder, common to them all, however, is an extensive failure of the affective or of the voluntary life In most cases, too, there is a more or less marked failure of the intellectual powers

The patients are subject to purposeless impulses and purposeless inhibitions Irregular impulses to movement may prove fatal, but in other cases there is an irremediable hebetude [dullness] and a failure of will power, as we see in the severest form of the disease, which is known as catatonia .

Persons suffering from a schizophrenic taint usually show slight mental anomalies before the actual outbreak of the disease We note in them a certain blunting of the affective and voluntary life On the other hand, in the families to which persons suffering from schizophrenia belong, we can usually detect the presence of "schizoid" psychopaths, who may never become affected, and indeed usually do not become affected, with well-marked schizophrenia Most of the persons who are commonly spoken of as "eccentric," persons who are shy, unsociable, self-centered, reserved, cold, and devoid of a sense of humor, belong to this category. The Bavarians have a way of saying that some one "is spinning," and the term applies aptly to these minor degrees of schizophrenia A schizophrenic condition may well be compared with spinning after the old style, the spinner being one who spends hour after hour twisting a thread, repeating the same movements over and over again and having no contact with the outer world For the schizoid psychopaths who wrap themselves up in their own qualities, a comparison to a caterpillar which invests itself in a cocoon of its own spinning may be regarded as apter still

Several types of schizophrenia are recognized· *hebephrenia*, characterized by unexplained smiling and laughter, introversion, hallucinations, and untidiness; *catatonia*, in which there is a loss of the desire to talk or move and a tendency to assume fixed postures, *paranoia*, distinguished by delusions of persecution, leading often to violent and criminal behavior.

According to Rosanoff, no anatomical change has been found in the brain of persons suffering with schizophrenia. Physiologically, it is probable that schizophrenia develops as a metabolic disturbance, since, as has

been discovered recently, the administration of repeated overdoses of insulin large enough to reduce the blood sugar to the point of shock and unconsciousness may remove the symptoms, especially if the treatment is begun in the early stages of the disease. Repeated electric shocks and the administration of the drug metrazol have similar beneficial effects

As to the heredity of schizophrenia, Lenz concluded from his review of the extensive studies of family histories in Germany that in all cases there is a basic hereditary predisposition This is the consensus of present students of the disease.

Dr Franz J Kallmann,[1] now of the Department of Medical Genetics of the New York State Psychiatric Institute, has also described numerous pedigrees of schizophrenia. He thinks that the susceptibility to it is inherited as a recessive. Good evidence for heredity as a factor has been

TABLE 25 SCHIZOPHRENIA IN TWINS*

Investigator	Year of analysis	Number of pairs		Percentage of concordance	
		Dizygotic	Monozygotic	Dizygotic	Monozygotic
Luxenburger	1930	60	21	3 3	66 6
Rosanoff	1934	101	41	10 0	67 0
Essen-Möller	1941	24	7	16 7	71.4
Slater	1951	115	41	14 0	76 0
Kallmann	1952	685	268	14 5	86 2

* From Kallmann

obtained from the study of twins Kallmann finds that among identical twins, if one twin develops the disease the other does so in 86.2 per cent of the cases, while only 14.5 per cent of fraternal twin pairs show concordance His data and those from other investigators[2] are shown for comparison in Table 25 Evidence for recessive inheritance is found also in the excess of consanguineous marriages among the parents of *schizophrenics.*

The fact that a considerable percentage of identical twins are not concordant is important, it proves that the environment, either prenatal or postnatal, may be the determining factor in a given pair. As to the nature of these environmental factors Kallmann[3] states that "If one twin remains completely free of schizophrenic symptoms or breaks down much later than the affected co-twin (or shows a far more benign type of psy-

[1] Franz J. Kallmann, "Heredity in Health and Mental Disorder," W. W. Norton & Company, New York, 1953

[2] Eliot Slater with the assistance of James Shields, Psychotic and Neurotic Illnesses in Twins, *Med Research Council (Brit.) Spec Rept Ser*, *No* 385, 1953

[3] F. J Kallmann, Applicability of Modern Genetic Concepts in the Management of Schizophrenia, *J. Heredity,* 39:339-344, 1948

chosis), there is always a difference between the twins in regard to physical strength and body weight from early childhood These differences in physique are consistently in favor of the more resistant twin " In Kallmann's cases the most frequent postnatal environmental factors favoring the development of schizophrenia were unusual physical or emotional strains, pregnancy, acute infections, and a drastic reducing diet The maintenance of weight seems to be of great importance in escaping schizophrenia and in recovery from it

There is some evidence that persons who are heterozygous are likely to show certain abnormal symptoms, that is, they are of the "schizoid type" Homozygotes who escape schizophrenia may also be of the schizoid type Judging from the rather high frequency of schizophrenia in the population the percentage of heterozygous carriers must be high

Manic-Depressive Psychosis

Rosanoff's definition of this mental disease is as follows:

> . . . a group of constitutional mental disorders in which the disturbances are primarily and mainly in the sphere of the emotions They are characterized by attacks of excitement, or depression, or of mixtures of the elements of both, each attack generally terminates in recovery, but leaves behind a tendency toward recurrence.

Kallmann's definition in his book cited above differs slightly:

> The essential diagnostic feature of the given classification was its restriction to cyclic cases which showed periodicity of acute, self-limited mood swings before the fifth decade of life and no progressive or residual personality disintegration before or after such episodes

During the depressive, or melancholic, phase the sufferer often seriously considers ending his own life as a means of escape from his mental suffering, and not infrequently does so William Cowper, famous English poet of the eighteenth century, who suffered several attacks of the disorder, attempted to take his own life and was saved only by an accident. Robert Mayer, great German physicist of the nineteenth century, discoverer of the law of the conservation of energy, who was a periodic victim of the disease, made a similar unsuccessful attempt. As is proved by the cases mentioned, and by others that could be cited, the disease does not spare those of superior mental ability Contrary to what many persons suppose, however, there is no proof of a positive correlation between genius and insanity [1]

As with schizophrenia, no evidence of pathological changes in the tissues of the brain has been discovered. Some authors think that the root

[1] E. M East, Insanity and Genius, *J. Heredity*, 29:275-279, 1938.

of the trouble may be a disturbance in the endocrine glands of a susceptible individual, brought on by some great loss or disappointment.

Many persons are subject to alternate moods of depression and elation of a mild degree, some much more than others The point at which this tendency ceases to be considered normal cannot be sharply defined

Manic-depressive psychoses are from one and one-half to two times as frequent in females as in males Kallmann reports that in contrast to schizophrenia, manic-depressive psychosis much oftener affects persons with a tendency to obesity and that several studies show about two-thirds of the cases are persons of the round-bodied (pyknik-endomorphic) type. The first attack usually occurs between 20 and 50; in persons past 50 the chance of an attack steadily decreases Its frequency among Europeans and Americans varies from about 0 4 per cent to 1 6 per cent of the general population

As to the mode of inheritance of manic-depressive psychoses, pedigree studies indicate dominance, with incomplete penetrance. Kallmann states that nearly 60 per cent of cases come from matings of one normal and one manic-depressive or cycloid parent, and that if unclassified persons are omitted and cycloid persons added to the clearly manic-depressive cases, the observed ratio of affected to unaffected sibs is 0 9:1, approximating the ideal ratio of 1 1

The deficiency in cases is readily explainable if an environmental factor—which may not make its appearance—is necessary for the development of the disease.

SPECIAL TALENTS

There are many special abilities, including mechanical ability, musical ability, and ability in other artistic lines, that are not measured by the ordinary "intelligence tests." Rosanoff says:

> Not a few subjects, who have a mediocre or even a subnormal intelligence, possess at the same time a high degree of mechanical ability . . . Some children display a strong interest in music and seem to be specially gifted with musical talent. There does not appear to be a high degree of correlation between musical ability and general intelligence, and quite outstanding musical ability has been *noted in subjects of mediocre and even subnormal intelligence, on the* other hand, subjects of very superior intelligence have been known to be totally lacking in musical appreciation or ability.

Conversely, persons of high intelligence and lively imaginations may have well-developed powers of appreciation of music with little or no inclination toward or ability in musical expression.

All that has been said of music probably could be said of other artistic lines—drawing, painting, and sculpture The relative independence of

mechanical and artistic aptitude applies primarily, however, to the imitative and performing phases of the arts, for there is no good evidence that a person of subnormal intelligence can become a great inventor, a great composer, or a great painter. The statement attributed to Turner who, in answer to the question as to what he used in mixing his paints, replied "brains," is probably true for all great creative artists

Musical Ability

Musical ability is far from being a single unit, but depends at least upon the following factors. (1) sense of pitch, (2) sense of loudness, (3) sense of time or rhythm, (4) sense of harmony, (5) sense of sequence of tone or melody, and (6) memory. These all exist as independently measurable capacities.[1,2] A successful composer must have, in addition to these, strong powers of imagination and the ability to put his mental creations on paper

In view of the complex nature of musical talent, we should not expect it to be inherited in any simple way That heredity is an important factor, however, is beyond dispute The early age at which special musical ability often makes its appearance, and the persistence of the urge to musical expression, frequently in the face of severe discouragements, is strong evidence of the hereditary factor The particular line of expression of the talent and the degree of its development depend, of course, to a large extent upon the immediate cultural surroundings and opportunities for expression.

Many pedigrees of musical families have been published, but since musical talent probably depends upon the cooperation of several genes, it is not surprising that such pedigrees offer difficulties of interpretation in Mendelian terms. One of the most noted of such pedigrees is that of the Bach family (Fig 136), published by Mjoen [3]

Apparently, little is known about the females in the early generations of the Bach pedigree, since they are not even indicated on the chart. A strong tendency for musicians to marry musicians, however, has long been known to exist, and this may have played a part in the piling up of musical ability in the Bach family Both of the wives of Johann Sebastian Bach (1685–1750) were musical Bach and his first wife, Maria, were second cousins, both having a great-grandfather in common in the male line From this marriage, 50 per cent of the children showed eminent musical ability. All 19 of Bach's children are indicated as more or less musical

It is interesting to note that Johann Sebastian Bach was the [illegible]

[1] Carl E Seashore, New Vantage Grounds in the Psychology of Music, [illegible] 84 517–520, 1936

[2] Carl E. Seashore, Science in Music, *Science*, 95:117–122, 1912

[3] Jon A Mjöen, Genius as a Biological Problem, *Eugenics Rev*, vol 17, [illegible]

member of a pair of identical twins, of whom Bach's son wrote, "They resembled one another so closely that even their wives could not tell them apart. . . . In speech, in mood, in everything, they were alike In music, too, you could not distinguish them, so like was their execution, so like their interpretation" (Lenz) This in itself is evidence of the part played by heredity in musical ability.

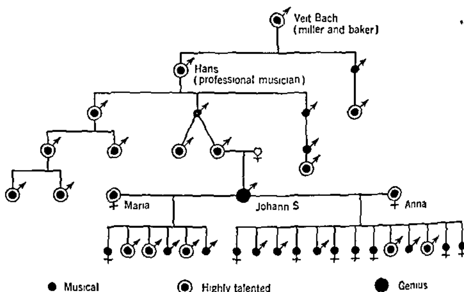


Figure 136. Pedigree of the Bach family through six generations, showing unusual musical talent. (*After Mjoen*)

Mjöen also gives a pedigree of the Mozart-von Weber family and one of the Backer-Lunde-Grondahl family, showing musical ability running through several generations, although on a less grand scale than in the case of the Bachs From his studies of these and many other families, Mjöen concludes in the following words:

> The higher the average talent of the parents, the higher the average talent of the children. In our material "very talented" parents have no "untalented" children, and "untalented" parents no "very talented" children

Regarding the manner of inheritance of musical talent, Mjöen states that his studies give little information.

Drawing, Painting, and Sculpture

Relatively little can be said about the inheritance of talent in the graphic and plastic arts Although inherited differences undoubtedly exist, they have received much less attention than in the case of music This is due in part to the much greater number of musicians than of

artists in other lines It is well known that the powers of discrimination with reference to color, line, and form and their graphic representation depend to a certain extent upon innate capacity, although of course these powers are highly influenced by training The existence of inborn differences is borne out by observation of very young children in their attempts to draw and paint Children who receive the same training in drawing, painting, and sculpture continue to differ markedly in their ability in these arts.

Pedigree studies for the graphic and plastic arts seem to be very few An early investigation by Francis Galton,[1] founder of the scientific study of human heredity, disclosed that the famous Italian painter Titian (1477–1576) had eight relatives who were good painters

Mathematical Ability

Special aptitude in mathematics seems to be inherited, often independently of ability in some other directions, such as ability in literary

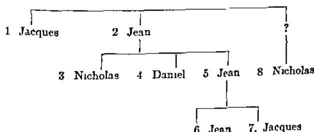


Figure 137. Pedigree of the Bernoulli family of mathematicians (*After Francis Galton*) For explanation see text

and philosophical expression. Occasionally, remarkable ability in rapid mental calculating—explainable largely as an innate capacity—makes itself evident at an early age

The Bernoulli family of Swiss mathematicians of the seventeenth and eighteenth centuries is noteworthy for the number of its members who made original contributions to mathematics According to Galton, there were eight men in this family in three generations, as shown in Fig. 137, who possessed special mathematical ability Five became members of the French Academy. One was early destined for the church and two for business, but they left these occupations to become mathematicians

Following Galton's account, the characteristics of the individuals in the pedigree are summarized briefly as follows

1. Jacques Early destined for the church. Accidentally became ac-

[1] Francis Galton, "Hereditary Genius," The Macmillan Company, New York, 1869

quainted with mathematics. Slow but sure A mathematician of the highest order in originality and power. Member French Academy.

2 Jean. Destined for commerce, but left it for science and chemistry. French Academy.

3. Nicholas A great mathematical genius.

4. Daniel. Physician, botanist, anatomist, writer on hydrodynamics; very precocious Obtained ten prizes French Academy.

5. Jean Jurisconsult, mathematician, and physicist. Obtained three prizes of the Academy. Member French Academy. Destined for commerce but hated it Loved oratory.

6. Jean Astronomer, mathematician, and philosopher. Wrote many works

7. Jacques Physician and mathematician Drowned at 30.

8. Nicholas Mathematician French Academy.

PROBLEMS

1. If marriages are at random with respect to the Rh factor, what is the chance that a marriage of Caucasoids in the United States will be such that the child may suffer from erythroblastosis?

2 What is the chance that a marriage of Negroes in the United States will be such that a child may suffer from erythroblastosis? Assume random matings with respect to the Rh factor

3. Make a list of normal human traits for which there is good evidence of Mendelian heredity. (By normal differences we mean those which are not pathological, that is, those that do not handicap the individual in his usual environment)

4 Suggest a reason for the fact that the most extreme types of hereditary defect in man which are either congenital or which develop in the first few years of life, e g, amaurotic idiocy, are recessive, whereas equally serious defects, e g, Huntington's chorea, which usually develop in middle life, are often dominant

5. Make a list of nonadaptive or neutral differences distinguishing the races of mankind (Consider traits listed in previous chapters also)

6. Make a list of adaptive differences between the races of mankind, i e, differences that fit their possessors to their respective environments

7. Name, if possible, two human races in which there is no overlapping with respect to some physical trait designated by you.

8. What is the fallacy in the following statement. Roughly three-fourths of the population of the United States are tasters of phenylthiocarbamide [a fact]; therefore the ability to taste this substance is dominant

9. Why is it especially difficult to prove genetic differences in behavioral traits in man?

17

IMPROVEMENT OF THE HUMAN SPECIES (EUGENICS)

In the chapter on Heredity and Evolution we expressed the view that man has it within his power to determine to a large extent his own biological future. This conclusion implies first of all that man shall have a conscious goal or ideal for his own species The goal of course may be a shifting one Have we, as a matter of fact, any common biological ideals for *Homo sapiens?*

IDEALS

Practically all people will agree that mankind, in the mass, is at present far from perfect Both physically and mentally there is much room for improvement. It may be worth our while to attempt a statement of the lines of improvement upon which most men would agree

Health. A condition of robust health, both physical and mental, surely is desired by everyone for himself and probably would be accepted as a desirable end for all mankind Adopting a broad definition of health, we may think of it as a state of well-being, adaptation, or fitness to the environment Good health thus implies the possession of sufficient strength and energy for the performance of all desirable activities and the attainment of happiness. It means freedom from all hereditary defects, weaknesses, or diseases which impair efficiency, prevent happiness, or unduly shorten life. Under the term health one should include beauty, since in the truest sense beauty is a by-product of good health. Superlative physical size and strength as universal human attributes are no longer either necessary or desirable. In modern times, with the rapid achievement of a mastery over the forces of nature, mere size and strength have yielded first place to mental ability.

Intelligence. However much we may differ in our appreciation of intelligence, few will deny that the ability to think and reason straight is one of the most adaptive qualities in man. This ability is obviously the trait of all traits that sets man above every other species. Without presuming that a high degree of intelligence is indispensable to individual

happiness, we could agree perhaps that the kind of happiness of which only the intelligent are capable is most to be desired A reasonably high level of intelligence in the average man, plus superior ability in numerous individuals, is essential for the maintenance of a high state of civilization.

Variability. No one who has given thought to the subject will contend that mankind would be more successful and happy if all individual differences were eliminated On the contrary, many advantages can be traced to the existing variability among human beings. The striking development of civilization in recent centuries has been possible only through a remarkable multiplication of specialized occupations. As a consequence, the need for special talents is greater than ever before If all people were cast in the same mold, human culture would suffer greatly. The popular expression that it takes all kinds of people to make a world rests upon sound biological principles That special talents have a strong hereditary basis has been indicated in the discussion of human heredity in Chap 16 In order to promote the general welfare, the state should encourage the multiplication of talented individuals

Moral Character. In the preceding editions of this book ethical, or moral, character was not specifically mentioned as one of the characteristics that most men would accept as an ideal for our species. This did not mean that the writer regarded moral character as secondary or as not subject to improvement Rather, it was assumed that the improvement in intelligence would naturally promote the improvement in moral character This assumption was based in part upon the results of many psychological studies in the United States and the British Isles which have shown a positive correlation between intelligence and moral character. However, let us now consider specifically for a moment improvement in the moral character of mankind.

The word *moral* has been given various shades of meaning. It will here be used to mean those qualities of the individual that express themselves by word or deed in all ways that tend to promote the good of the species Consistent moral behavior grows out of sympathy, or fellow feeling. In a species with a history such as ours moral behavior can hardly exist without this friendly emotion. Given the feeling of satisfaction that comes from doing what is good for one's fellow men and the intelligence to know what is good for them, the genetic improvement of mankind would seem to follow of necessity.

Whether the progressive evolution of *Homo sapiens* is to be our supreme end or ideal is a philosophical question that we need not now consider. At our present stage of knowledge of the universe we know of no other intelligent species on any other planet than our own. Our ignorance, of course, is no evidence that intelligent and evolving beings do not exist on other planets somewhere in the universe. Whether or not

there ever arises the problem of a conflict of loyalties between a love of our own species and a desire to promote the progress of evolution wherever it may be operating in the universe cannot now be told To the writer there is no apparent conflict between unlimited loyalty to man and loyalty to any supreme design or designer that one may discover in the universe. This of course is only the expression of the conviction that the evolutionary progress of mankind is a part of any design that may exist. If the foregoing premises are accepted, the conclusion seems to follow that moral character based upon intelligence and fellow feeling is the highest ideal that we can have for man, because with such a character man has the means for endless progress toward perfection.

RACIAL DIFFERENCES

So far, we have been speaking of individual differences without regard to race. The term *racial difference* is here used in the strict zoological sense to mean a hereditary difference that is characteristic of a group of individuals originally occupying a particular geographical region A racial difference need not apply to all of the individuals within the group, since by definition races are not reproductively isolated from each other wherever their ranges meet, cross-mating may take place, with the resultant commingling of genes Differences that develop during the life of the individual as the result of differences in environment or training are not true racial differences Like one's own language, such differences are not racial in our present sense Unfortunately for clear thinking, the word *race* is frequently used in a very different sense by people who speak of the English race, the Irish race, the Jewish race, and so on. The differences among these and similar groups do not meet the zoological test of race.

Beyond all doubt there are racial differences with respect to the ability to live and thrive in particular environments The dark-skinned peoples of the tropical and subtropical zones, for example, are better fitted to endure the strong sunlight of their natural habitat than are the white-skinned peoples Consequently, with respect to pigmentation, there is no common ideal for all mankind Similar considerations apply to differences in adaptation to the extremely cold climates of the arctic regions or to extremely high altitudes in the Andes and the Himalayas In these extreme conditions local tribes have become specially adapted to the cold or to the rare atmosphere Many of the differences between races, however, such as skull shape and facial features, are of no known adaptive significance They add variety and interest to life, and no good reason is apparent for wishing them eliminated. Differences between races in such important traits as health and intelligence in so far as these are geneti-

cally determined are probably relatively insignificant as compared with the tremendous variations in these respects within a race Measurements of intelligence and special aptitudes have so far failed to bring out any clear-cut hereditary racial differences, although the problem of devising tests of innate ability free from the complicating effects of environmental differences has not been solved It is therefore not justifiable to state dogmatically, as some have done, that there are no such differences Whatever differences may exist in average and range could be demonstrated only by careful statistical methods. It is certain that the application of such methods will reveal great overlapping in the curves of variability, whatever they may turn out to be.

It seems clear that the points of likeness among races far outnumber and outweigh their points of difference. The greatest progress for mankind as a whole, therefore, would seem at present to consist in the raising of the level of health, energy, and intelligence within each race, rather than the forcible supplanting of one race by another. This is especially true in view of our ignorance regarding the gene make-up of the various racial groups. In so far as we can apply to *Homo sapiens* the principles of evolution discussed in Chap 14 we may conclude that the continuation of biological progress is best served by the retention of numerous racial stocks, each race being free to develop along its own lines, with opportunities for frequent interchange of ideas and products and for periodic intermarriages The present partial isolation of racial groups permits the testing of various combinations of traits under a variety of conditions. Migration and intermarriages afford opportunity for the emergence of new and favorable combinations of traits

METHODS OF IMPROVING MANKIND

Few subjects have aroused more controversy than the question of methods for improving the genetic quality of mankind. Should we concentrate our efforts on the improvement of the environment, trusting that the improvement of the species will naturally follow; or should our sole concern be the grading up of hereditary capacities? In the discussion that follows we shall attempt to show that both of these ideas should enter into the formation of our policy and that the greatest progress will come from a combination of the two.

Among the English-speaking peoples the science dealing with the genetic improvement of mankind is known as *eugenics*, a word introduced by a famous English scientist, Francis Galton, in 1885; the term is derived from the Greek *eugenes*, meaning "well born." Galton's definition is as follows: "Eugenics is the science which deals with all influences that improve the inborn qualities of a race; also with those that develop them

to the utmost advantage." As defined by Galton, eugenics obviously is a science deriving its content and principles both from genetics and the social sciences An excellent short biography of Galton, with an account of the development of eugenics in the British islands, has recently been published by an eminent English physician, who for many years was secretary of the Eugenics Society founded by Galton [1]



Figure 138 Francis Galton, 1822–1911 (*From Pearson, "The Life, Letters and Labours of Francis Galton," Cambridge University Press*)

Restrictive Measures, Negative Eugenics. The application of eugenic principles, whether going under the name of eugenics or not, follows one of two lines. first, the discouragement of matings between individuals representing types considered undesirable; and second, the encouragement of matings between desirable types The first of these is known as negative eugenics; the second is known as positive eugenics

1. *Marriage Restrictions* Since ancient times organized society has taken an active hand in determining the genetic constitution of the pop-

[1] C P. Blacker, "Eugenics: Galton and After," Harvard University Press, Cambridge, Mass , 1952

ulation. Various tribal customs and laws tending to prevent the reproduction of specific types, or favoring reproduction among others, have been extant at one time or another. We have referred already to such laws in connection with cousin marriages (Chap 13). Today the marriage of certain types of mental defectives, epileptics, habitual criminals, alcoholics, insane persons, and persons infected with venereal disease is prohibited in many of our states

2 *Segregation.* The common practice of segregating mental defectives and mentally diseased persons in institutions obviously has an effect similar to laws preventing their marriage. Unfortunately, large numbers of mental defectives are allowed their unrestrained freedom, with the result that defective children are born to them. Criminal laws requiring the imprisonment or execution of individuals whose conduct is destructive, incidentally, have similar selective effects, even though eugenic motives are not the primary ones in the enactment of criminal laws

The effectiveness of isolation of undesirables as a method of improving the hereditary quality of the population depends, of course, upon the extent to which the undesirables owe their misfortune to heredity. In our consideration of the problem of heredity and environment in Chap 11, and heredity in man in Chap 16, it became clear, however, that heredity is one of the factors responsible for mental defect, mental disease, and abnormal behavior Leading investigators are agreed on this point. In a very readable book, Dr. L S Penrose,[1] of University College, London, has presented an excellent summary and analysis of the evidence.

3. *Sterilization* As an added means of preventing the reproduction of undesirable or dysgenic types, a majority of our states, as well as a number of foreign countries, have legalized surgical *sterilization* The prescribed operation consists in tying off and severing the ducts that conduct the sperms and the eggs from the gonads In the male the operation is a simple one, done under a local anesthetic; in the female the usual procedure involves a major abdominal operation. The gonads themselves are not disturbed, and no part of the body, except a small section of the sperm ducts or egg tubes, is removed; consequently sterilization has no effect upon secondary sexual characters or sex impulses, in these respects differing entirely from castration. In only a few states is castration legalized [2]

Sterilization laws have been criticized adversely on several grounds, and competent geneticists are not agreed as to their desirability. Aside from the objection to them by many persons on religious grounds, the

[1] Lionel S Penrose, "The Biology of Mental Defect," Grune & Stratton, Inc , New York, 1949.

[2] J. E. Hughes, Eugenic Sterilization in the United States: A Comparative Summary of Statutes and Review of Court Decisions, *Public Health Repts. U.S , Suppl.* 162, 1940

point has been made that their enforcement constitutes a violation of personal liberty; that they are subject to danger of grave abuse, and that, after all, the objectives sought may be accomplished just as effectively by segregation during the reproductive years There is undoubtedly in most persons a natural and well-founded repugnance to the placing of hands upon the person of another, against the other's will, even though such action is carried out under sanction of law From the humane point of view, the burden of proof as to the desirability of sterilization, therefore, would seem to rest upon the advocates of the measure It should be emphasized that in our country sterilization operations are done ordinarily only with the consent of the patient or, in case he is mentally incompetent, of his guardian. Frequently, however, the alternative is continued confinement in an institution

Society undoubtedly has the right as a matter of self-defense to prevent the increase in numbers of grossly defective types which would either become a burden on the state or a menace to others To give the individual his choice of confinement or sterilization may, in certain cases, be more humane than to require him to remain in confinement In the United States the legal grounds for sterilization usually are restricted to mental disease, mental deficiency, epilepsy, and habitual criminality, whereas in some foreign countries sterilization is prescribed in cases of gross physical defect or where the probability of transmission of such mental or physical abnormality is great. In many of our states the law has become almost a dead letter.

Prior to 1950 there were 50,707 cases of sterilization officially reported from all the states, of which 39 per cent were carried out in California In 1949 California led the states with 381 sterilizations; North Carolina came next with 249; then in order Virginia, 215, Georgia, 167, and Iowa, 165 Mental deficiency was the chief reason for 916 of the operations, psychosis for 477, and other causes for 77.[1]

Genetic Variables. The effectiveness of marriage restrictions, segregation, and sterilization as eugenic measures depends upon several variables: (1) upon the manner in which the undesirable trait is inherited; (2) upon the frequency of the gene or genes concerned in the population; (3) upon the age at which the trait makes its appearance; and (4) upon the extent to which the environment may prevent the expression of the gene First, as to mode of inheritance, let us consider the following possibilities·

1 The trait is due to a dominant gene

2 The trait is due to a gene without dominance (heterozygote intermediate).

[1] C. J Gamble, A Progress Note on Eugenic Sterilization in the United States, *Eugenical News*, vol 35, 1950

3. The trait is due to a sex-linked recessive gene.
4. The trait is due to an autosomal recessive gene.
5. The trait is due to two or more dominant genes, two or more recessive genes, or to some combination of these.

The easiest trait to weed out of the population is the one due to a *single dominant gene* or to a gene in which dominance is lacking The prevention of reproduction of all affected individuals, that is, those showing the trait and those recognizable as carriers, in a single generation will eliminate the gene from the population, provided it is a trait that always develops before sexual maturity and provided the gene is one that always expresses itself. New mutations to the same allele will, of course, probably occur The frequency of the trait in the population thereafter will be determined by the frequency of mutation Since everyone carries a pair of genes at each locus in his chromosomes (excepting the sex chromosomes in males), the incidence of the trait will continue at double the mutation rate for the gametes. For example, if the rate of mutation to a particular allele of a gene is one in 50,000, the frequency of the dominant trait will be one in 25,000.

In the case of highly deleterious dominant traits that develop before the reproductive age is reached, most affected persons will represent new mutations Natural selection will keep such traits at a low frequency without the application of eugenic measures

With dominant traits that develop during or after the age of reproduction, as with Huntington's chorea (Chap. 16), the reduction of the trait will proceed more slowly. In a grave and fatal disease of this type the brothers and sisters, as well as the children, of affected persons would be wise to refrain from becoming parents, since their chance of carrying the gene is 50 per cent.

The second easiest type of trait to deplete in the population is the *sex-linked recessive.* Since males have only one X chromosome while females have two, approximately a third of all sex-linked genes in the population at any one time are present in males and two-thirds are present in females Furthermore, in males the effect of a sex-linked gene is always manifest, since there is lacking any normal counteracting allele (This of course assumes that the sex-linked gene is not suppressed by the environment or other genes.) The isolation or sterilization of all affected males will, therefore, eliminate one-third of the defective genes in a single generation. If like treatment is applied to both males and females, the only remaining genes will be those carried in the heterozygous condition by females. In the succeeding generation, due to the mechanism of sex determination, approximately half of these genes will be found in males In this generation the prevention of mating of affected males, therefore, will reduce the supply of the gene in question by one-half. Through a continuation of the process the percentage of persons showing the trait will

be cut 50 per cent in each generation; hence, in a few generations it will be reduced to the vanishing point, except for the occurrence of mutations.

In case natural selection against a sex-linked recessive trait is severe, as in hemophilia (Chap. 14), the gene will never become very numerous in the population.

Traits due to *autosomal recessive genes* may be reduced in frequency *only* at a much slower rate than dominants and sex-linked recessives. This conclusion follows from the fact that males as well as females may be heterozygous for autosomal genes. The higher the frequency of an autosomal recessive trait the more rapidly it may be reduced by the restrictive measures we are discussing. If the trait is extremely rare, existing say in the order of one in 20,000, as in the case of albinism, restriction of affected individuals will have very little effect, because most affected persons are produced in marriages of two heterozygotes. In the case of albinism, if we assume that the gene is distributed at random throughout the population, about one person in 70 must be a carrier of the gene. If matings are at random, the proportion of marriages capable of producing an albino is

$$\frac{1}{70} \times \frac{1}{70} = \frac{1}{4,900} \text{ (one in 4,900)}$$

If the recessive trait is lethal or if it prevents reproduction, the frequency of the trait will approximate the rate of mutation.

The elimination of traits that depend upon the cooperation of *two or more genes* is the most difficult of all. Here even a dominant gene may go unrecognized since the trait develops only in the presence of some complementary gene. The complexity of the genetic situation in such cases has been considered in the discussion of the factor principle (Chap. 6).

With traits that are influenced strongly by environment, as well as by genes, e.g., manic-depressive psychoses and schizophrenia, there is an added difficulty in applying restrictive measures. Under any system of negative eugenics likely to be adopted, genetically defective individuals who for one reason or another escape the symptoms are certain to escape detection. The most effective reduction of such traits seems to require the additional use of positive measures, particularly education.

Positive Eugenics. Among the measures which may well have the effect of increasing the frequency of desirable traits are the following.

1. Regulation of immigration
2. Subsidizing superior individuals
3. Education
4. Promotion of genetic research
5. Improvement of environmental conditions

Let us consider each of these briefly in the order given.

1. *Immigration* It is obvious that immigration is one of the factors that may affect the frequency of particular genes in a population and thus influence evolutionary changes Nations customarily regulate by law the number and quality of their immigrants The reasons behind the laws are usually based on a mixture of economic, cultural, and biological motives

The laws of the United States exclude entirely certain classes of immigrants including the feebleminded, insane, epileptics, narcotic-drug addicts, chronic alcoholics, psychopathic personalities, and sex perverts, persons afflicted with tuberculosis in any form, leprosy, or any dangerous contagious disease; persons likely to become a public charge because of a physical defect, disease, or disability; persons who have been convicted of a crime involving moral turpitude, other than a purely political offense, or who admit having committed acts constituting the essential elements of such a crime, also narcotic-law violators or illicit traffickers in narcotic drugs, polygamists, prostitutes, and procurers, illiterates (persons over 16, physically capable of reading, who cannot read and understand any language or dialect), anarchists and those who advocate totalitarian-dictatorship forms of government or the overthrow of the government by force and violence.

As we have seen in previous chapters, heredity is a factor in many of these undesirable types. In many cases cultural and economic reasons can also be given for their existence.

The United States immigration laws also place a limit on the number of persons of any one nationality who may be admitted annually Those admitted cannot exceed a certain percentage (1/6 of 1 per cent) of the number of persons of the same origin resident in the United States in the year 1920 There are exceptions to this rule, limiting to 100 the number admissible annually from specified Asiatic and African countries and areas The above quotas do not apply to countries in the Western Hemisphere, except as regards persons who possess 50 per cent or more of "Asiatic blood" For further details the reader is referred to a nontechnical summary of United States laws and regulations on immigration.[1]

The quota provision is obviously a conservative factor in that it favors the immigration of racial types and cultural patterns already predominant in the population Regarding the wisdom of this part of the law there is a lack of unanimity among citizens of the United States Good eugenic reasons could be given for admitting immigrants who meet high standards of health, intelligence, and moral character regardless of national or racial origins.

2. *Subsidizing the Fit.* Little has been done in this country with the

[1] Carol M. Crosswell, "A Guide to Admission to the United States. Immigration Laws of the United States," 2d ed , Oceana Publications, New York, 1953.

avowed object of encouraging the reproduction of especially well-adapted individuals In only a few organizations are selected workers granted a bonus for the birth of children. According to Professor S J Holmes, of the University of California, one of the leading students of eugenics in this country, the proper distribution of allowances for the birth of children is one of the most feasible of all the methods ever advanced for the promotion of positive eugenics.[1] As an illustration of what might be accomplished along this line, he cites the following case.

Foreign missionaries in the Baptist and Congregational churches receive a fairly substantial allowance for each child, so that the financial burden of a large family is in many cases no greater than that of a small one This may explain the facts that the families of these missionaries are considerably larger than those of ordinary ministers, and that the missionary birth rate has shown little decline for several years.

In this country family allowances are granted to officers in the armed services and the Coast Guard, and in some cases in the Public Health Service. The Salvation Army makes family-allowance grants to its officers The principle has been applied to teachers in a few public schools and colleges On the contrary, in some of our public school systems a penalty, consisting in loss of position or loss of salary, is attached to the birth of a child. In other systems, for example in the Chicago public schools, special maternity leaves are granted to women schoolteachers Presumably such provisions as the exemption clause in the Federal income-tax law, allowing an added exemption for each child, is a step in the right direction. Competitive scholarships in colleges and universities have a similar beneficial effect, since concern over the problem of providing an education for the children is one of the motives for voluntary limitation of family size.

3. *Education.* A knowledge of the fundamental principles of genetics, with special reference to human heredity, and an appreciation of desirable attitudes and ideals undoubtedly affect the actions of young persons in the choice of mates From the point of view of the happiness of the individual, as well as that of the welfare of the state, no type of learning has greater possibilities. Education in the principles of heredity need not be limited to the schools, but may be carried on through other agencies including the church, the theater, the popular press, the radio, and television, provided always that persons engaged in such educational activities are thoroughly grounded in the science of genetics.

The family physician is in a strategic position to serve his patients by informing them in matters of heredity. Unfortunately, the training of

[1] Samuel Jackson Holmes, "The Eugenic Predicament," Harcourt, Brace and Company, Inc , New York, 1933.

physicians in this field has lagged. The condition is being remedied to some extent in progressive schools of medicine, but much still remains to be done. A good course in genetics, with special reference to man, is highly desirable for all medical students.

The education of the people to the advantages of keeping family records and consenting to autopsies, in all cases involving doubt as to cause of death at least, will work for the best interest of the family and of the state In this sphere as much as in any other, only knowledge of the truth can make men free

4 *Promotion of Genetic Research.* The basic principles of heredity respecting the distribution of the genes are now known. A good beginning has been made in the analysis of the roles of heredity and environment in the development of characteristics in the organism. The mechanism of the inheritance of many specific traits in man can be clearly stated If the knowledge we now possess could be applied intelligently to the improvement of man, much progress might be made. However, genetics is still a new science, and research is yielding and will continue to yield large dividends for some time to come. The problem of the physiological action of the genes is one of those now receiving intensive study. With a more complete knowledge of the nature and action of the genes, the possibilities of regulating their effects in the interests of the individual will be increased. The question of the nature of mutations and their possible control is largely one for future research

Genetic research on plants and animals is today receiving much support from the Federal and state governments and from privately endowed institutions A few American institutions are making significant contributions to research designed directly for the genetic improvement of mankind, and the number is growing. Among these are the following:

The American Genetic Association, publishers of *The Journal of Heredity*, Washington, D C.; The Genetics Society of America; The American Society of Human Genetics, publishers of *The American Journal of Human Genetics*, The American Eugenics Society, publishers of *Eugenics Quarterly;* the Department of Genetics of the Carnegie Institution of Washington, Cold Spring Harbor, Long Island, New York; The Dight Institute for Human Genetics of the University of Minnesota; Roscoe B Jackson Memorial Laboratory, Bar Harbor, Maine; the Heredity Clinic of the University of Michigan; the Laboratory of Human Genetics of the University of Utah; and the medical schools and departments of zoology in a number of the leading universities.

Direct support of eugenic research by Federal and state governments would seem to fit the part of enlightened self-interest, since the genetic improvement of its citizens is of the highest advantage to the state.

5 *Improvement of Environmental Conditions* We think usually of eugenics as concerned with the improvement of the hereditary qualities of the people It should be emphasized once again, however, that a characteristic as such is not inherited; all that we inherit is the tendency to develop certain characteristics under particular environmental conditions Consequently, heredity has no meaning apart from the environment

In any plan to increase the fitness of the organism, whether it be a plant, a domesticated animal, or man, due regard must be had to the environment in which the organism is to live If one is interested, for example, in the production of beef, or in the development of speed in a race horse, he places his animals in the environment that he desires as their permanent one. The food and care are the best he is able to devise for the end in view. Selection then is made on the basis of performance under the prescribed set of conditions. It would not show good judgment to spend one's time breeding a strain of beef cattle or race horses able to survive on the poorest food or in the most polluted atmosphere or under the greatest extremes of temperature, although by selection a strain could be developed that would be superior to existing breeds in enduring any one or perhaps all of these adverse conditions

Obviously, we should look upon the improvement of man in a similar light Unless the environment is made as nearly optimum as possible for all the people, we are not giving all of the genetically superior individuals an opportunity to express themselves. The inability to survive under extremely adverse conditions does not necessarily mean the inability to survive under modern civilization Many of the conditions endured by our ancestors have now become artificial so far as we are concerned· we do not anticipate a return to them In any effort designed to improve the adaptation of human beings we should be concerned primarily with the present and the future.

A study of the principles of genetics leads one to believe that neither the extreme environmentalist nor the extreme advocate of heredity has any justification for his position. Both look at only one side of the shield.

CONCLUSION

Each of the highly desirable traits—vigorous h
character, and special talent—probably depends
Some of these genes are dominant, some are recessi
dominance. For the full expression of these traits
ment is necessary In view of the complex nature of
heterozygous constitution, we should expect to see
defective children produced by superior parents. New

count for some of these, but the majority are the result of segregation, independent assortment, and recombination. Conversely, and for similar reasons, we should not be surprised to see many superior individuals produced by mediocre parents. Two average parents may each contribute genes lacking in the other to obtain a child of unusual ability. The great number of persons of average ability is an important factor in explanation of the large number of superior children produced by average parents. Nevertheless, superior parents have a better chance of producing superior children than do mediocre or defective parents.

A steady increase in the number of children from the better-adapted parents should result in a gradual rise in the average quality of the population. Evolution in nature is a slow process. The best we can hope for in man is that application of eugenic measures will cause a slow but steady improvement. The problem is far more complex than the development of a pure breed of domesticated animal where complete control of matings is available and where a uniform type is the goal. Many generations will probably be necessary to bring about a notable change in man. The slowness of the process, however, need not discourage us if we but recall that man most certainly is near the beginning of his history. Before him lies a future too vast for the mind to comprehend. Barring cosmic accidents, there is apparent no good reason why man may not anticipate a billion years of life on earth. Who knows indeed but that man will prove to be the one species able to avoid the extinction which in time overtakes all species.

It is inconceivable that as time passes man will fail to apply to himself more and more the proved biological principles suited to his own improvement. As he improves himself genetically he will of course constantly seek to make the environment more and more suitable to develop the best that is in him. If the logic in the foregoing pages is sound, the conclusion seems inescapable that our biological ideals for man are well within the bounds of reason, assuming that we shall have the intelligence, the will, and the perseverance to apply the knowledge which investigators have made available, and will continue to make available, in the days to come.

PROBLEMS

1. Mention some of the methods used in developing a pure breed of animals that are not directly applicable to the improvement of man.

2. List five practicable means of improving the hereditary constitution of a people.

3. List some of the laws, customs, and conditions in the United States which tend to reduce the force of natural selection by *favoring* the reproduction of individuals poorly adapted to take care of themselves and their children.

4. List some of the laws, customs, and conditions in the United States that act as selective agencies by *hindering* the reproduction of individuals poorly adapted to take care of themselves and their children.

5 Mention several advantages in late marriages with respect to the genetic improvement of mankind Mention several disadvantages in this respect

6. Give several specific examples of hereditary characteristics in man which are adaptive under a given set of primitive conditions but which are either useless or disadvantageous under modern conditions of civilization

7 How do you account for the extremely great range of hereditary mental capacity *within* a race of people as compared with the relatively smaller range existing *among* the various races?

8. Give several reasons why it is very difficult to show racial differences with respect to mental traits Does the difficulty in demonstrating such differences mean that no racial differences in mental capacity exist? Explain

9. Discuss the possibility of the final emergence of a single human race to replace the several races now in existence on earth, mentioning factors now favoring such a change as well as those tending to hinder it

10 List the advantages and the disadvantages that might result from the changes mentioned in Problem 9

18

DOMESTICATED PLANTS

The absolute dependence of civilized man upon domesticated plants and animals for his living tends to make us forget that at one stage in human evolution our ancestors had no domesticated species at all. Man was exclusively hunter and food gatherer for a much longer period of time than he has been herdsman and planter Domestication did not come suddenly, nor in any one place. Slowly over the centuries, extending back long before historic times, man learned to take under his own care a few of the plants and animals around him which he found most pleasing and useful.

Every continent has contributed valuable domesticated species For a number of reasons Asia leads in important contributions; but in the modern world the place of origin is not of prime importance. Under modern conditions of rapid communication and transportation, the fruits of man's labors in this field have become available to planters and breeders all over the earth Wherever a domesticated plant or animal will thrive, there we are not surprised to find it.

It was domesticated plants that Mendel used for the discovery of the basic laws of heredity. Darwin set a high value on the study of domesticated plants and animals for the solution of problems of evolution; the first chapter in his "The Origin of Species" dealt with this topic. Nine years after the publication of this classic he brought out as his next major work, a two-volume treatise on "The Variation of Animals and Plants under Domestication" In it he condensed a wealth of information derived from his exhaustive reading, wide observation, and extensive experiments with domesticated species The present writer wishes to recommend this work because of its great interest and value as a document on the history of domestication. It is here also that Darwin developed in full his hypothesis of pangenesis, which he hoped would explain the inheritance of acquired characters. It is evident that he had not read Mendel's paper on peas Pangenesis and the inheritance of acquired characters both proved to be illusions.

Following the rediscovery of Mendel's paper, at the beginning of the

present century, domestication took a new and fruitful turn. Great economic benefits have come from the application of the principles of modern genetics to domesticated plants and animals, as illustrated in the production of hybrid corn The practical results of domestication have in turn served to stimulate many new advances in genetic theory.

In this chapter we shall consider ten of the leading crop plants of the world All have been studied more or less intensively by geneticists, and numerous Mendelian characters have been found in each

WHEAT (*Triticum*)

Wheat originated in the Near East and the Mediterranean regions It has become the leading crop plant of the world The genus *Triticum* is classified into numerous species Those commonly listed, grouped according to the number of chromosomes, are as follows

Group 1 (7 pairs of chromosomes, diploids)
- *T. boeoticum* (wild einkorn) (= *aegilopoides*)
- *T monococcum* (einkorn)

Group 2 (14 pairs of chromosomes, tetraploids)
- *T carthlicum* (Persian wheat)
- *T. dicoccoides* (wild emmer)
- *T. dicoccum* (emmer)
- *T. durum* (durum, or macaroni, wheat)
- *T orientale* (Khorasan wheat)
- *T. polonicum* (Polish wheat)
- *T. pyramidale* (cone wheat)
- *T timopheevi* (timopheevi)
- *T. turgidum* (poulard, or rivet, wheat)

Group 3 (21 pairs of chromosomes, hexaploids)
- *T. aestivum* (common, or bread, wheat) (= *vulgare*)
- *T. compactum* (club wheat)
- *T. macha* (macha)
- *T. spelta* (spelt wheat)
- *T. sphaerococcum* (short, or Indian dwarf, wheat)

Hybrids produced by crossing diploids with members of both of the other groups are sterile. Hybrids between tetraploids and hexaploids are largely fertile. Wheat is normally self-fertilizing

Most of the wheat grown in the United States is either common wheat or durum There are many varieties of these, especially of common wheat. The varieties differ among themselves in one or more Mendelian char-

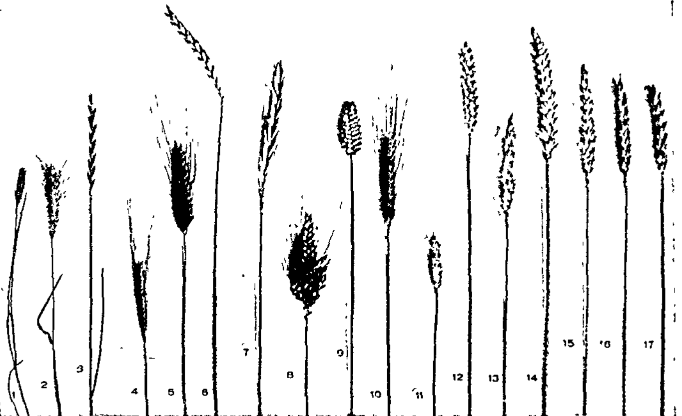


Figure 139. Variations in the heads of wheat and other grasses. (1, 2, 3) Wild grasses related to wheat. (4) Einkorn. (5) Emmer. (6) Spelt. (7) Polish wheat. (8) Poulard wheat. (9) Club wheat. (10) Durum wheat. (11) Turkey wheat. (12) Wilhelmina wheat. (13) Pacific bluestem wheat. (14) Dicklow wheat. (15) Marquis wheat. (16) Red fife wheat. (17) Kitchener wheat. (*Courtesy of Chicago Natural History Museum.*)

acters Some of these characters that have been most thoroughly analyzed in tetraploid and hexaploid wheats are as follows

Mendelian Characters in Wheat

Symbol	*Character*
a	awnedness (bearded); in some crosses heredity complex
al	albino
Ba	black awns
Bg	black heads
Bh	branched heads; in some temperatures and length of day, dominant
Bk	blue grain
Br	resistance to bunt (stinking smut)
C	compactness of head (club wheat)
El	elongate glumes, as in Polish wheat, incomplete dominance
Em	early maturing, in some crosses hybrid intermediate
Er	ergot resistance
Fl	flinty grain
Hd	hooded awn
Hg	hairiness of glumes
Hl	hairiness of leaf
Hn	hairiness of nodes
Ho_1, Ho_2, Ho_3	hollow stems (3 separate genes, cumulative effect)
Hr	Hessian fly resistance
K	keel on glumes
lg	liguleless
Lr	leaf rust resistance (many genes)
Mr	mildew resistance
Pa	pinkish anther
q	"squarehead"—short rachis internodes in upper part of spike
$R_1R_2R_3$	red grains (3 additive genes), white recessive
Ra	anthocyanin in auricle of leaf sheath
Rc	red coleoptile
Rg	red glumes
Rs	red straw
sa	smooth awns
sg	winter habit of growth, in some crosses inheritance complex
Sh	shattering
sp	sphaerococcum character—short culms, compact spike, nearly spherical heads
Sr	stem rust resistance (many different genes)
s	virescent
W	waxy layer on stem and leaves
Yg	golden-colored plant

In addition to the characters listed above there are others of a more-or-less nature (quantitative characters) that depend upon gene differences. Some of these, such as lodging, narrow leaf, tall straw, and thick straw, are complex in their genetics, hence not so easily worked with in breeding and experiments.

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OATS (*Avena*)

Oats are of Old World origin. About 18 species of the genus *Avena* have been described. Grouped according to chromosome numbers the most commonly mentioned species are:

Group 1 (7 pairs of chromosomes, diploids)
- *A. brevis* (short oat)
- *A. nudibrevis* (small-seeded, naked oat)
- *A. strigosa* (sand oat)
- *A. wiestii* (desert oat)

Group 2 (14 pairs of chromosomes, tetraploids)
- *A. abyssinica* (Abyssinian oat)
- *A. barbata* (slender oat)

Group 3 (21 pairs of chromosomes, hexaploids)
- *A. byzantina* (cultivated red oat)
- *A. fatua* (common wild oat)
- *A. nuda* (naked, or hull-less, oat)
- *A. sativa* (common white, or northern, oat)
- *A. sterilis* (wild red, or animated, oat)

Crosses are easily made between species having the same chromosome number. Crosses between 14 and 28 chromosome species produce fertile seeds only when the 28-chromosome species furnishes the egg. Crosses between 14 and 42 chromosome species rarely succeed and then only when the 42-chromosome species provides the egg. Crosses between 28 and 42 chromosome species are fertile with either parent as the pollen producer. The explanation of the infertile crosses is the abnormal behavior of the chromosomes during meiosis. Oats are normally self-fertilizing.

Sampson states that the common cultivated oat (*A. sativa*) is generally believed to have arisen from *A. fatua*. But he considers that a final decision cannot yet be given on the origin of the hexaploid cultivated oats. Oats were grown in Europe from 2000 B.C. on.

Coffman has summarized the evidence from genetics, cytology, physiology, and pathology for the origin of the common cultivated oat (*A. sativa*) as well as other cultivated oats in America from the wild red oat (*A. sterilis*).

Mendelian Characters in Oats

Symbol	*Character*
ar	articulated (fatua) type of upper grain
Aw	awnless type; *aw*, strong-awned type (dominance incomplete)
Aw_1	awnless type; aw_1, weak-awned type (dominance incomplete)
B	black grain, *b*, nonblack
C	covered grain; *c*, hull-less grain (dominance incomplete)
D	dwarf
d_1	dwarf
Dg	deep-gray grain; *dg*, light-gray grain (dominance incomplete)
fa	fatuoid type; *Fa*, normal (dominance incomplete)
G	gray grain; *g*, white grain
Gl	glabrous rachilla, *gl*, hairy rachilla
go	golden—yellow as seedlings, turning greenish at maturity
ha	hairless at base of lower grain, *Ha*, short hairs
L	ligules present
Lg	long-haired glumes, *lg*, glabrous glumes
Lh	long hairs at base of lower grain
N	nonarticulated base of lower grain (dominance incomplete)
P	pubescent back of the lower grain
pu	pubescent base of upper grain
R	red grain, *r*, nonred (yellow, white)
Rc	resistance to crown rust
Rl	resistance to loose smut
Rs	resistance to stem rust
rs_1	resistance to stem rust
Rt	resistance to covered smut
Sh	short-haired glumes, *sh*, glabrous glumes
Sp	spreading pannicle, *sp*, side pannicle
Wa	waxy lemma (incomplete dominance)
Y	yellow grain; *y*, white

(Other characters, which depend on two or more genes, are listed by Matsuura.)

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BARLEY (*Hordeum*)

Barley, a cereal of Old World origin, is one of the widely grown crop plants of temperate regions all over the earth. In the genus *Hordeum* there are numerous species, with many subspecies and cultivated varieties. All domesticated species have seven pairs of chromosomes; wild species with 7, 14, or 21 pairs are known. According to Smith, writing in his excellent comprehensive review of the cytology and genetics of barley, it is the small number of chromosomes and the large number of clearly classifiable characters that have made barley one of the six leading species of plants in the number of gene loci plotted on linkage maps.

Barley is normally self-fertilizing, but occasionally cross-fertilization takes place naturally in growing fields. Some varieties (naked) cross more frequently than covered varieties. Experimental cross-pollination, including the crossing of different cultivated species, has been done by many investigators. Most of the hybrids are fully fertile. The number of Mendelian characters that have been reported is unusually large.

Mendelian Characters in Barley[1]

(Roman numerals indicate linkage groups.)

Symbol		*Character*
a	I	albino seedling
a4	I	albino seedling
a5	I	albino seedling
a_b	V	albino seedling
a_c	VI	albino seedling
a_{c2}	III	albino seedling
a_n	VI	albino seedling
a_t	II	albino seedling
al	I	liguleless
B	II	black lemma and caryopsis
B^g	II	gray lemma and caryopsis
B^{mb}	II	medium-black lemma and caryopsis
be		branched ear (duplicate factors)
Bl	IV	blue aleurone (complementary factor)
Bl2	III	blue aleurone (complementary factor)
br	VII	brachytic
bt	II	brittle rachis
cr		curved peduncle
D		dwarf (sterile)
da	I	dehiscent awn
e	I	elongated (awned) outer glume
e2		fine-awned outer glume
Ea	I	early maturity (several factors)
er		erectum base on grain (complementary factors)
er2		erectum base on grain (complementary factors)

[1] Largely after Smith, abridged

Symbol		*Character*
f	I	chlorina seedling
f_s	VII	chlorina seedling
fs	V	fragile stem
G	I	teeth on lemma
gr		glaucous ear
Gh		glumes, hairy
gl	IV	glossy seedling
gp		grandpa
Gr	VI	growth factors
Gs		glaucous sheath
H	I, III	high (tall)
H2	V	high (tall)
HI		high (tall), modifying factor
hg		susceptibility to *Helminthosporium gramineum*
Hl	I	susceptibility to *H sativum*
Hl2	II	susceptibility to *H sativum*
Hl3	V	susceptibility to *H sativum*
Hr	I	hairy rachis
Hr2	V	hairy rachis
Hs		hairy leaf sheath
I	IV	infertile intermedium
I^h	IV	fertile intermedium
I_1		third factor for fertility of the lateral floret
j		complementary factors inhibiting red pericarp color
j2		complementary factors inhibiting red pericarp color
K	IV	hooded
kl	III	long-awned
kw	I, VII	kernel weight (multiple factors)
L	I, III, IV	lax spike
Lb	V	long basal internode
lc	III	long chromosomes
lg	I	light-green seedling
lg2	IV	light-green seedling
lk	I, III	length of awn
lk2	1, III	series of factors for awn length
Log	I	long outer glume
lp		lethal progeny (complementary factors)
lr	I	lateral spikelet appendage on lemma reduced
m		many-noded dwarf
Ml_a	II	susceptibility to mildew
Ml_b	II	susceptibility to mildew
Ml_g	IV	susceptibility to mildew
ms2	I	male sterile
mu		multiploid sporocytes
n	III	naked
o	V	orange lemma
or	I	orange seedling
P	I	purple lemma
P_e	I	purple-veined lemma
pa	I	susceptibility to *Puccinia anomola*

Symbol		*Character*
Pbg	III	pubescence on outer glume
Pr	I	purple straw
R	V	rough awn
Rt	III	rough awn
ra	V	rachilla short
rb		ribbon grass (streaked leaves)
Re	V	red pericarp
Re2	I	red pericarp
rin	I	rachis internode number
rin2	IV	rachis internode number
Rs	III	red stem
rt		rattail spike
s	V	short rachilla hairs
sc		susceptibility to *Fusarium* scab
Sh	V	spring habit of growth
t	VII	susceptibility to *P. graminis tritici*
tr	I	triple-awned lemma
trd	II	third outer glume
tw	I	tweaky
U		unbranched styles
uh		susceptibility to *Ustilago hordei*
un	VII	susceptibility to *Ustilago nuda*
uz	VI	semibrachytic
v	I	six-rowed
V^t	I	allele for *deficiens*
V^d	I	two-rowed
V	I	two-rowed
w	I	wide glumes
Wh		waxy bloom on head
Wh2		waxy bloom on head and stem
wi		wide glume inhibitor
Wl		waxy bloom on leaves
Ws		weakly (attached) spikelet
wx	VII	waxy endosperm
x		xantha seedling
x_c	VI	xantha seedling
y	I	virescent seedling
yc	VII	virescent seedling
z	IV	zoned leaf

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INDIAN CORN (*Zea mays*)

Indian corn, or maize, is a New World plant of very ancient origin. The great pre-Columbian civilizations of the Americas—Maya, Aztec,

Inca—were founded upon an agriculture in which maize was the chief food plant. The Spanish explorers of the late fifteenth century found the Indians growing many varieties of maize One of these, known as pod corn (Fig. 140), bears seeds that are enclosed within the glumes Mangelsdorf and Reeves give a very interesting discussion of pod corn as a possible ancestor of modern *naked corn* No single wild species can be identified as the ancestor of *maize*, although numerous explorations have been



Figure 140. The earliest printed illustration of the heterozygous form of pod corn Reproduced from Bonafous' classical monograph "*Histoire naturelle, agricole et economique du Maïs,*" 1836 (*Courtesy of Harvard University*)

made with the aim of discovering a wild maize The several rival theories on the origin and evolution of maize usually involve a *combination of selection* and hybridization Following the discovery of the American continents at the close of the fifteenth century maize spread widely throughout Europe, Asia, and Africa; it is now a competitor of rice as the second leading crop plant of the world, wherein wheat ranks first.

The widespread cultivation and ease of crossbreeding of corn have made it the most thoroughly analyzed of all plants from the genetical point of view. In the latest comprehensive catalogue of Mendelian characters in maize, compiled by Weijer, approximately 500 genes are listed Maize has 10 pairs of chromosomes (Fig 42). Many of the 500 genes have been assigned to particular chromosomes; the locus for about 100 genes

is known—these loci are indicated by the numbers preceding the gene symbols in the following list of characters.

Linkage Groups in Corn[1]

(Numbers in column at left indicate gene loci as determined by crossover percentages.)

	Symbol	*Character*
		CHROMOSOME 1
0	*sr*	striated leaves—fine longitudinal striations during life of plant
15	ga_4	gametophyte factor
25	ms_{17}	male sterile–17
27	ts_2	tassel seed—tassels bear seeds
28	*P*	pericarp and cob color—a large series of alleles for pericarp and cob color
30	*zl*	zygotic lethal
53	*as*	asynaptic—partially sterile
59	*hm*	helminthosporium resistance
75	*br*	brachytic—short internodes, plant ⅓–½ normal height
79	*rg*	vestigial glumes
80	f_1	fine stripe–1 leaves—white tissue on margins of leaves
102	an_1	anther ear–1—staminate flowers only on ear
123	*Kn*	knotted leaf
129	gs_1	green-striped–1 leaves—light-green stripes
152	Ts_6	tassel seed–6—tassels bear seeds
156	bm_2	brown midrib–2
		CHROMOSOME 2
0	ws_3	white sheath
4	*al*	albescent—seedling green, turning white later
11	lg_1	liguleless leaf–1
30	gl_2	glossy seedling–2
49	*B*	booster—intensifier of plant color
56	*sk*	silkless—female sterile
68	fl_1	floury endosperm—*fl fl Fl*, floury, *Fl Fl fl*, normal
74	ts_1	tassel seed–1—no pollen, seeds on tassel
83	V_4	virescent seedling–4—seedlings yellowish green
128	*Ch*	chocolate pericarp—dark-brown pericarp
		CHROMOSOME 3
0	cr_1	crinkly leaves—leaves broad, crinkled at base
18	d_1	dwarf plant—plant about ⅓ normal height
32	*rt*	rootless—secondary roots few or absent
38	lg_2	liguleless leaf–2
40	*Rg*	ragged leaves—plant weak, leaves split and torn; incomplete dominance
47	ts_4	tassel seed–4—a few seeds in the tassel
64	ba_1	barren stalk—no pistillate flowers
75	na_1	nana plant—dwarf plant, ⅓–¼ normal height
103	a_1	anthocyanin—colorless aleurone, brown pericarp
115	*et*	etched aleurone
121	ga_7	gametophyte factor

[1] After Rhoades.

	Symbol	Character

Chromosome 4

0	de_1	defective endosperm–1
35	Ga_1	gamete-differential fertilization
56	Ts_5	tassel seed–5—silks and anthers in tassel
66	sp_1	small pollen
71	su_1	sugary endosperm
74	de_{16}	defective endosperm–16—lethal
84	zb_6	zebra-striped
100	*Tu*	tunicate ear (pod corn)—glumes enclose individual kernels, *Tu Tu* usually sterile; *tu tu*, naked seeds
105	j_2	japonica–2—variegated striping
111	gl_3	glossy seedling–3

Chromosome 5

0	a_2	anthocyanin–2—A_2, a factor in plant and aleurone color
6	*bm*	brown midrib
7	bt_1	brittle endosperm—usually shrunken
10	v_3	virescent–3—seedlings light yellow, turning green quickly
12	*bv*	brevis—plants usually about ½ normal height
31	*pr*	red aleurone; *Pr*, purple
40	ys_1	yellow stripe–1—leaves striped yellow between vascular bundles
72	v_2	virescent seedling–2—very light yellow, turning green slowly

Chromosome 6

0	*po*	polymitotic—microspore cells undergo several meiotic-like divisions without division of the chromosomes, no pollen produced
13	*Y*	yellow endosperm
33	*pg*	pale-green seedlings
44	*Pl*	purple plant color
45	*Bh*	blotched aleurone, expression variable
54	*sm*	salmon-colored silk
64	*py*	pigmy plant—small, with short, thick, striated leaves

Chromosome 7

0	o_2	opaque endosperm—little or no corneous starch
4	*in*	intensifier of aleurone color
8	v_5	virescent seedling–5—seedlings greenish yellow, turn green quickly
22	ra_1	ramosa ear–1—ear branched at base, conical
26	gl_1	glossy seedling–1
36	*Tp*	teopod—plant strongly tillered, narrow leaves; many small podded ears
40	*sl*	slashed leaves—leaves split and torn longitudinally
42	*ij*	iojap striping—variegated strips
60	*Bn*	brown aleurone
96	*bd*	branched silkless—ears branched at base

Chromosome 8

0	v_{16}	virescent–16—seedlings very light yellow; turn green slowly
14	ms_8	male sterile–8—no anthers exerted, microsporocytes usually degenerate
28	j_1	japonica–1-stripe—variegated striping, does not show in seedlings

	Symbol	*Character*
		CHROMOSOME 9
0	*Dt*	dotted aleurone
7	yg_2	yellow-green-2—seedling and plant yellowish; viability poor
26	*C*	aleurone color—in appropriate genotype gives purple or red aleurone
29	*sh*	shrunken endosperm
31	*bz*	bronze anthocyanin
41	*bp*	brown pericarp—in presence of *P* gives brown pericarp
59	*wx*	waxy endosperm—starch stains reddish brown with iodine, instead of blue
71	v_1	virescent seedling-1—seedlings yellowish, become green quickly
		CHROMOSOME 10
0	*Rp*	rust resistance—resistance to form 3 of *Puccinia sorghi*
16	*Og*	old-gold stripe
28	*li*	lineate stripe—older leaves only show fine longitudinal stripes
38	*lg*	luteus—yellow seedling
43	g_1	golden plant-1—yellowish green in plants, may show in seedling in strong light and high temperature, viability good
57	*R*	anthocyanin—in appropriate genotypes gives purple or red aleurone and red or purple plants

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RICE (*Oryza sativa*)

Rice is one of the three leading food plants of the world. In production it is equal to maize and is clearly exceeded only by wheat. Rice is the staple diet of about half of the people on earth. It leads all other cereals in the two most populous countries of the world, China and India, as well as in Korea, Japan, and the countries of southeastern Asia. Its place of origin is India, where there are several wild species of the genus *Oryza*, and where domesticated rice also grows wild as a weed. Domesticated rice is a highly variable plant, with a great many named varieties, all of which are placed in the one species *O. sativa*.

Rice was among the first of the plants to be studied from the point of view of Mendelian genetics: most of the experimental work has been done in Japan, India, and the United States. Many clearly segregating

characters have been identified The gene symbols used for the characters have differed among the authors. The symbols given below follow Nagao, of the Plant Breeding Institute, Hokkaido University, Sapporo, Japan, and Jodon, of the Rice Experiment Station, Crowley, Louisiana Most of the characters listed depend upon single gene differences with complete dominance. In some cases, however, there is interaction of several genqs Nagao describes in detail his theory of the development of anthocyanin colors through the complex interaction of the alleles at the C, Sp, and Rp loci

Rice has 12 pairs of chromosomes Relatively few cases of linkage have so far been established.

Mendelion Characters in Rice

Symbol	*Character*
al	albino
An	awnedness
ans	awned sterile
bc	brittle culm
bs	barren sterile
$C^B, C^{Bp}, C^{Br}, C, c$	chromogen (anthocyanin)—5 alleles, complementary to alleles at *Sp* locus
ch	chlorina
clk	claw-shaped hull
Cl	clustered spikelets
cs	complete sterile
cps	compact-panicle sterile
Ce	resistance to *Cercospora oryzae*
d	dwarf (general)
d_1	daikoku dwarf
d_2	ebisu dwarf
d_3, d_4, d_5	tillering dwarf, triple recessive gives many tillers, very short
d_6	lop-leaved dwarf
da	double awn
dn	dense, or compact, panicle
df	dark furrows
ex	exsertion of panicle (partly enclosed or hokamuri)
F_{gr}	fragrant flower
fk	floating habit
Fl	flowering period
fs	fine-striped—greenish-white stripes on leaves of seedling
frs	female sterile
G	grain length (short versus long)
gl	glutinous endosperm
go	glossy leaf blade (hairy versus glossy)
gs	green-and-white-striped
gy	green-and-yellow-striped
Hm	resistance to *Helminthosporium oryzae*
IC	inhibitor of chromogen

Symbol	*Character*
IPl	inhibitor of purple leaf blade
IAn	inhibitor of awning
IRg	inhibitor of dark gold
la	lazy, or ageotropic
Le	resistance to *Leptoapoeria callanei*
Ld	lodging
lg	liguleless
lng	long empty glumes
Lp	long panicle
lu	lutescent
Ly	lemon yellow (palea and lemma)
Me	resistance to Melanosperma
mg	mottled green (momigare)
Ms	minute spikelet
mp	multiple pistil
ms	male sterile
ne	sinuous neck
og	oval grain
op	open spikelet
ops	open-spikelet sterile
P	anthocyanin coloration (general)
pas	paleaceous sterile
Ph	positive phenol reaction
Pi	resistance to *Piricularia oryzae*
Pl	purple leaf blade
Pla	purple leaf apex and margin
Plm	purple midrib (purple leaf axil)
Pls	purple leaf sheath
Pn	purple node
Pnl	purple internode
Pp	purple pericarp
Pr	purple root
Ps	purple stigma
Rb	ripening brown
Rc	brown pericarp (chromogen or chromophelein of red rice)
Rd	red pericarp (distribution of pigment produced by *Rc*)
Rg	ripening gold
Rl	ripening black
Rp	colored palea and lemma due to anthocyanin distribution
s	sterility (general)
Sg	spreading (motsure)
Sh	shattering
Sp,*Sp*[d],*sp*	colored apiculus, 3 alleles, complementary to *C*
ss	semisterile
sts	staminoidal sterile
tw	twisted leaf (lack of midrib)
th	triangular hull
to	tough-shelling
v	virescent
xa	xantha (lethal yellow)

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PEAS (*Pisum sativum*)

The edible garden pea is a native of Persia The pea is among the oldest of domesticated plants Crane and Lawrence state that peas were cultivated in England before the Norman Conquest (1066) It is reported that the sweet wrinkled pea was common in London markets in 1813.

Many plant breeders had experimented with peas before Mendel began his famous experiments in 1856 Numerous varieties were available to Mendel Since the rediscovery of Mendel's work in 1900 his experiments have been repeated on a large scale and fully confirmed Many additional genes have been discovered in peas

Mendelian Characters in Peas

(Linkage groups III and IV should possibly be combined)

Symbol		*Character*
A	VI	basic anthocyanin color of flower and seed coat, *a*, white
ar		violet flowers
ap		apple-blossom-pink flowers
am		pinkish-white flowers
b	III	rose, or salmon-pink, flowers
Bl	V	bloom or wax, *bl*, waxless (emerald)
Bt^a	I	blunt pods, bt^a, acute } Both dominants required to make pods blunt-ended (stumpy)
Bt^b	I	blunt pods; bt^b, acute }
Cp	VIII	straight pod, *cp*, curved pod
em^1, em^2		"emergences" if both are present
Da		pigmented axils, single ring, *da*, no pigment in axils
Db		pigmented axils, double ring, *db*, single ring
F		purple dotting of seed coat I
F_s		purple dotting of seed coat II
fa		fasciated stem, flowers terminal
fe		split pods, sterile as female
Fl		gray spotting on leaves, *fl*, green leaves
Fu		resistant to *Fusarium* wilt, *fu*, susceptible
G		green cotyledon, *g*, yellow cotyledon
Gp	VIII	green pod; *gp*, canary-yellow pod
H		with *A*, orange seed coat
I	II	inhibits action of *G*, giving dominant yellow cotyledons; *i*, green
If		intermediate flowering, *if*, early flowering
J		in presence of *A*, gives dark-brown seed coat

Symbol		*Character*
K	V	normal wings, *k*, keeled wings
La		short internodes, dwarf, *la*, long internodes
Lb		short internodes, dwarf, *lb*, long internodes (*la* and *lb* together, very long internodes, plants taller than *Le*)
Le	VII	long internodes, tall plants, *le*, short internodes, dwarf
Lf	VI	retards flowering time with *lf*, ineffective with *sf*, dominance incomplete
M	IV	with *Z* gives "ghost marbling" of testa, with both *A* and *Z*, brown marbling
n	VI	leaves narrow, pointed, elongated, small
O	II	green pods, *o*, creamy yellow pods
P	VII	thin parchmented membrane lining pod, *p*, without a membrane ("sugar" pods)
P_1	III	purple pod I } Both dominants necessary to make pod purple
P_2	III	purple pod II } Both dominants necessary to make pod purple
Pl		black hilum ("black-eyed"), *pl*, light hilum
R	I	round seed, *r*, wrinkled seed
re		reduced leaves
S		seeds free in pod, *s*, seeds adhere ("brochette")
st	III	stipules reduced
t	I	leaves in place of tendrils (acacia); dominance incomplete
un	IV	unifoliate, no tendrils
V	VII	with *P*, strong membrane lining pod, *v*, with *P*, thin membrane ("sugar" pods)
W		testa uniformly colored, *w*, testa spotted or lacking pigment
wb		white foliage, white plants die in seedling stage
w_2		white variegated leaves
Z		colored seed coat, *z*, uncolored seed coat

Flower Colors in Some of the Possible Anthocyanin Gene Combinations[1]

Purple	*AA ArAr BB ApAp AmAm*
Violet	*AA arar BB ApAp AmAm*
Rose (salmon pink)	*AA ArAr bb ApAp AmAm*
Light purple	*AA arar bb ApAp AmAm*
Apple-blossom pink	*AA ArAr BB apap AmAm*
Apple rose	*AA ArAr bb apap AmAm*
Apple violet	*AA arar BB apap AmAm*
Pinkish white	*AA ArAr BB ApAp amam*
White	*aa ArAr BB ApAp AmAm*

[1] After de Haan

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TOMATOES (*Lycopersicon*)

There are several species of tomatoes, all native to South America; each has 12 pairs of chromosomes. Most domesticated varieties are de-

rived from *Lycopersicon esculentum*. The tomato was introduced into Europe in the sixteenth century. On the Continent it was used as a food, but in England for some time it was grown only as an ornamental plant

During the past four centuries hundreds of varieties have been developed Some of these were produced through interspecific hybridization, which can be done readily in the genus *Lycopersicon* The tomato has given rise to a large number of mutations Several qualities of economic importance, such as fruit size, productivity, and earliness of ripening, depend upon multiple factors, individual genes in such cases may have small effects. Symbols have not been given for these

In most of the genes listed below dominance is complete or nearly so A few are given that involve gene interaction, e g , genes affecting fruit color, stem color, and size of plant.

The variety Marglobe is proposed by Barton et al as the standard, or normal, type with which the mutants are compared.

Mendelian Characters in Tomatoes[1]

(Roman numerals indicate linkage groups)

Symbol		*Character*
a (a_1)	V	anthocyaninless, stems and leaves always lack purple color, *A*, purple stem
ad		resistance to *Alternaria* collar rot
ag		anthocyanin gainer, purple pigment appears on cotyledons and lower sides of leaves when growth is slow
al (a_2)	VIII	anthocyanin loser, purple stems become green in 10 to 21 days
an		anantha, flowers greatly modified, inflorescences compound, closely resembles ca
ap		apetalous flowers, corolla reduced or absent, pollen scarce and nonfunctional
as_1		asynaptic meiosis, high pollen and ovule sterility
as_2		asynaptic meiosis; high pollen and ovule sterility
as_3		asynaptic meiosis, high pollen and ovule sterility
as_4		asynaptic meiosis, high pollen and ovule sterility
as_5		asynaptic meiosis; high pollen and ovule sterility
at		apricot or yellow-pink color of fruit flesh
aw		without anthocyanin; same phenotype as *a*
B		high β-carotene; low lycopene
bk	I	beaked; fruits with sharp points at stylar end
br	III	brachytic, internodes shorter than normal
bu	VI	bushy, internodes and inflorescences shortened, long petioles
c	IV	potato leaf, reduced number of leaf segments
ca		cauliflower, extremely branched inflorescences, aborted flowers
cb		cabbage, large dark-green leaves, fewer locules
Cf_1 (Cf_{sc})		resistance to races 1 and 3 of *Cladosporium fulvum*
Cf_2 (Cf_{p1})	IV	immunity to races 1 to 4 of *Cladosporium*
Cf_3 (Cf_{p2})	V	resistance to races 1 to 4 of *Cladosporium*
Cl_1		cleistogamous; flowers fail to open

[1] After Barton et al.

Symbol		*Character*
cl_2		cleistogamous, flowers open slightly
d (d_1)	I	dwarf, all parts foreshortened, leaves dark and rugose
d^x		extreme dwarf, recessive to d and d^+
dl		dialytic, stamens not united, hairs partially suppressed
dm (d_2)	IX	dwarf modifier, with d causes extreme dwarfing
dv		dwarf virescent, pale green at growing point, changes quickly to normal green, plant always stunted
e (b)		entire fewer leaf segments and distorted midvein
el (e)		elongated fruits as in Oxheart
ex		exserted stigmas, or styles twisted within anther tubes
f	V	fasciated, many-loculed fruits as in Ponderosa
fl		fleshy calyx, sepals often curled
(G)		inhibits modifiers, permitting expression of r
g		grooved fruits, may be associated with fasciation
gs		green stripes in epidermis of unripe fruit, golden in ripe fruit
H	VII	hairs absent except on hypocotyl and at growing point
hl		hairless no hairs on hypocotyl or rest of plant
I		immunity to race 1 of *Fusarium lycopersici*
j	V	jointless pedicles, calyx left on plant when fruit picked
(K)		inhibits modifiers, permitting expression of t
l	VI	lutescent, yellowish unripe fruits, premature yellowing of leaves
Lc		locule number reduced, associated with o
(lc_1,lc_2,lc_3)		control *locule* number
lf	V	leafy, indeterminate inflorescences
lg		light-green foliage
m	I	mottled, leaves and cotyledons with flecks of paler green
mc		macrocalyx, sepals leaflike and greatly enlarged

(The 18 *ms* mutants are *male-sterile* in that they deviate from normal only in the absence or extreme scarcity of functional pollen, parent variety is stated.)

ms_1		pale, shrunken anthers, no pollen; hybrid stock
ms_2		pale, shrunken anthers, no pollen, Pearson
ms_3		very pale, shrunken anthers; collapsed pollen mother cells; San Marzano
ms_4		pale, shrunken anthers; a few aborted pollen grains; Early Santa Clara
ms_5		abnormally small flowers, very pale and greatly shrunken anthers, usually no pollen, San Marzano
ms_6		shrunken, pale anthers, no pollen; San Marzano
ms_7		nearly normal-colored, slightly shrunken anthers; aborted pollen in tetrads, San Marzano
ms_8		abnormally small flowers with exserted stigmas, pale shrunken anthers, no pollen, San Marzano
ms_9		anthers nearly normal, no pollen; San Marzano
ms_{10}		abnormally small flowers, small, very pale anthers; greatly exserted stigmas, no pollen; San Marzano
ms_{11}		very pale, shrunken anthers; aborted pollen, free or in tetrads, San Marzano
ms_{12}		abnormally small flowers, nearly normal-colored but shrunken anthers, no pollen, San Marzano
ms_{13}		nearly normal anthers; free aborted pollen; San Marzano

bol		Character
		very pale, shrunken anthers, aborted pollen, Earliana
		abnormally small flowers with exserted pistils, very pale, dwarfed anthers, no pollen, San Marzano
		pale, shrunken anthers, clumped aborted pollen, Pritchard
		pale, shrunken anthers, no pollen, Ace
		exserted stigmas, slightly pale, very shrunken anthers, no pollen, Cal-255
		midget, all parts of plants reduced, high sterility
	X	nipple tips at stylar end of fruits
		narrow cotyledons, slow growth
	I	Necrotic; with Cf_2 causes progressive necrosis of leaves
	I	ovate or pear-shaped fruits
)		spherical, oblate, and elongate fruits
		ovate; elongate fruits with low locule number
	I	peach, dullness and increased hairiness of fruit epidermis
		sticky fruit epidermis
		pistillate, flowers usually lack stamens and are otherwise modified
		propellerlike cotyledons, true leaves greatly modified
		positional-sterile, corolla does not unfurl, pollen is not shed
	II	yellow color of fruit flesh
		rolled cotyledons
		ridged or rough leaves
		rosette, extremely short internodes, no flowers
		reticulate virescent, cotyledons and new leaves pale with dark veins, turning to normal green with age
	I	compound inflorescence, greatly increased number of flowers
		Septoria resistance
		stamenless, stamens usually absent, modified fruit form
		Stemphylium resistance
	IV	self-pruning, determinate plant habit
		sterile, completely sterile, plants later become purple
	VII	tangerine, orange color of fruit flesh and stamens
		trifoliate, leaf with usually only three segments and long petiole
	VII	uniform; unripe fruits of uniform light-green color without usual darker green cap at stem end
		uniform gray-green, as of *u* except for grayish color
		virescent, white seedlings
		Verticillium resistance
		vegetative, greatly deformed, usually functionless flowers
		villous, stems very hairy
		wiry, slender, threadlike leaflets, dwarfed plants
		wilty dwarf, grayish-green, droopy leaves, stunted plants
	II	white flower, corolla color is buff, light tan, or white
	I	woolly, all parts densely pubescent, homozygous lethal
	X	wilty, leaf margins curl adaxially
		ineffective microgametes associated with *I*
	VII	xanthophyllic, yellow leaves, retarded growth; homozygous lethal
	III	colorless fruit epidermis, *Y*, yellow skin
		yellow seedlings, lethal in early stage
		yellow virescent; new foliage is pale yellow-green, turning to normal green with age

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COTTON (*Gossypium*)

From the economic point of view cotton is the most important of the fiber-producing plants. Cotton seems to have originated both in the Old World and in the Americas. The multitude of domesticated varieties trace back to centers of origin in southern Asia, Australia, northern Africa, Mexico, or Central and South America. The first domesticated cotton may have been grown in India some four thousand years ago.

There are numerous species of cotton, as indicated in Knight's table below. The *genome* of each species is composed of 13 chromosomes. Each genome is represented by a capital letter. The three types of cotton grown in the United States are of New World origin. These are *Gossypium hirsutem* (upland cotton), *G. barbadens* (Sea Island cotton), and *G. tomentosum* (American-Egyptian cotton). Each of the three has 26 pairs of chromosomes, composed of two different genomes, the result of crossing (allotetraploids). The Old World species have 13 pairs of chromosomes.

The writer is greatly indebted to Dr. R. L. Knight, author, and to the Commonwealth Agricultural Bureau, Farnham Royal, England, publisher, for permission to copy the following material on cotton from their book "Abstract Bibliography of Cotton Breeding and Genetics, 1900–1950," Technical Communication 17 of the Commonwealth Bureau of Plant Breeding and Genetics, 1954. In his book Knight has abstracted all major papers on cotton published between 1900 and 1950—1,191 in all. His table of genomes and the gene list include data published after 1950 in order to make the information as up-to-date as possible.

Mendelian Characters in Cotton[1]

The Genomes of *Gossypium**

Species	*Genome*	*Species*	*Genome*
Asiatic and *African* ($n = 13$)		*American* ($n = 13$)	
G herbaceum	A_1	*G thurberi*	D_1
G arboreum	A_2	*G. armourianum*	D_2
G anomalum	B_1	*G harknessii*	D_2
G triphyllum	B_2	*G klotzschianum*	D_3
G stocksii	E_1	var *davidsonii*	D_3
G somalense	E_2	*G aridum*	D_4
G areysianum	E_3	*G raimondii*	D_5
		G gossypioides	D_6
Australian ($n = 13$)		*G hirsutum*	$(AD)_1$
G sturtii	C_1	*G barbadense*	$(AD)_2$
G robinsonii	C_2	*G tomentosum*	$(AD)_3$

*In the above table the classification used by Hutchinson, Silow, and Stephens (1947) has been adopted. The genome symbols are based on Beasley (1942), Stephens (1947), Douwes (1951 and 1953), Brown and Menzel (1952), and Douwes and Cuany (1952)

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[1] From Knight.

GENE LIST FOR *Gossypium*

Symbol suggested	Original symbol if different	Gene effect	Species
as_1		double recessive is asynaptic	*hirs*
as_2			*barb*
B_1		blackarm resistance	*hirs.* (*barb*)
B_2		blackarm resistance	*hirs* (*barb*)
B_3		blackarm resistance	*punct* (*hirs*) (*barb*)
B_4		blackarm resistance	*arb.* (*barb*)
B_5		blackarm resistance	*barb.*
B_{6m}		blackarm-resistance intensifier	*arb* (*barb.*)
B_7		blackarm resistance	*hirs* (*barb*)
b_8		blackarm resistance	*anom* (*arb*)
Bp	B^P/B^S	pitted boll	*barb*
bw		withering bracts	*hirs.*
chl_1	$y_1\ c^{ha}$	double recessive is chlorophyll-deficient	*hirs.*
chl_2	$y_2\ c^{hb}$		*barb.*
chl_1		chlorophyll-deficient	*herb.*
chl_2		chlorophyll-deficient	*arb*
ck^X		corky (complementary)	*hirs*
ck^Y			*barb.*
cl_1	d	cluster	*hirs*
cl_2		Egyptian short branch	*barb*
cl		short branch	*herb.*
clg		cleistogamy	New World
Cr^N		full normal } distinguished only in hets with cr^D	*barb.*
Cr^n		low normal	*hirs*
cr^r		*rugose*	*hirs.*
cr^D		crinkled dwarf	*barb*
cr^C		contorta	*barb*
Cp_a	A	crumpled (complementary)	*arb*
Cp_b	B		*arb. herb stock. tril*
cr		crinkled	*barb hirs*
cr	cra	crinkled	*arb.*
cu		curly	Old World
d		female-sterile dwarf	*arb*
d_1	d_a	double recessive is dwarf-bunched	*hirs.* (*barb*)
d_2	d_b		*hirs* (*barb.*)
d_1	d_a	Anakapalle dwarf	*arb.*
d_2	d_b	Cocanada dwarf	*arb*
d_3	Db	dwarf	*herb.*
de_1	de_a	incomplete boll dehiscence (de_1 is epistatic to de_2)	*herb*
de_2	de_b		*arb.*
de_3		closed boll	*herb*
Fbr	B^r	brown fuzz } green epistatic to brown	*hirs.*
Fgr	G	green fuzz	*hirs*

GENE LIST FOR *Gossypium* (*Continued*)

Symbol suggested	Original symbol if different	Gene effect	Species
Fm	S^m	little fuzz	*barb*
Fn	Ab N 1	naked seed, low lint index	*hirs*
fr_1		frilly (duplicate)	*hirs*
fr_2			*hirs*
Ft/ft	T/t	tufted seed/naked	*barb*
Fz/fz	F^t/f^t	tufted seed/fuzzy	*hirs*
Fz/fz	T/t	tufted seed/fuzzy	*arb*
g		no ovary	Old World
H_1	H^{TA} H^B	hairy leaves	*barb hirs herb*
H_2	H^{TO}	tomentose leaves	*tom hirs* (*barb*)
H^m		superstellate hairs	*herb*
h_a	h^G	glabrous lintless	*arb*
h_b		glabrous lintless	*arb*
l		broad leaf	*arb herb*
L		narrow leaves	*arb*
L^A		*anomalum* lobe	*anom*
L^B		mutant broad leaves	*arb.*
L^I		mutant intermediate leaves	*arb*
L^L		laciniate leaves	*arb*
L^N		narrow leaves	*arb*
L^O	O^O/o^n	okra leaf	*hirs*
L^S	O^S/o^n	super-okra	*hirs*
Lc_1^K	K^H	khaki lint	*hirs*
Lc_1^K	K_1 K	khaki lint	Old World
Lc_1^M		cauca mahogany lint	New World
lc_2	k_2	white lint	Old World
Lc_2^B	D_1	light-brown lint	Old World
Lc_2^K	K^B	khaki lint	*barb*
Lc_2^K	K_2	khaki lint	Old World
Lc_2^M		medium-brown lint	Old World
Lc_2^V		very light brown lint	Old World
Lc_3^B	D_2	light-brown lint	Old World
Lc_4^K		khaki lint	*arb.*
Lg	G^1	green lint	New World
li_a		hairy lintless	*herb.*
li_b		hairy lintless	*herb*
li_c	H^L	hairy lintless (sometimes lethal)	*arb*
li_d		hairy lintless	*herb*
li_e		hairy lintless	*arb*
li_{sh}		short lint (epistatic to li_e)	*arb*
li_{sp}		sparse lint	*arb*
lm		immature lint	*arb*
lr	r^1	round leaf	*hirs*
ls	s	single-lobed leaf	*arb*
m_1	m	increased no of floral parts	*arb.*

GENE LIST FOR *Gossypium* (*Continued*)

Symbol suggested	Original symbol if different	Gene effect	Species
m_2	m^b	multibracteolate	*herb.*
ne		leaf nectaries absent	*tom.* (*hirs.*)
ne		leaf nectaries absent	Old World
p_a		pollen color P_aP_b yellow, p_aP_b cream, P_a	Old World
p_b		p_b pale	Old World
Pdy	Fpd	petalody	*arb*
ple		pistillate	Old World
R_1^{RO}	R^{II} R^{I}	red plant body	New World
R_1^{ARM}	S^{ARM}	*arm* petal spot	*arm.* (*hirs.*) (*barb*)
R_1^{ARI}	S^{ARI}	*arid* petal spot	*arid* (*hirs*) (*barb*)
R_2^{AF}	S^f	tinged stem + full petal spot	*barb*
R_2^{AL}	S^l	tinged stem + intermediate spot	*barb*
R_2^{AO}	S^o	tinged stem, spotless	*hirs*
R_2^{ASB}	S^s R_2^{AS}	tinged stem + full spot	*barb*
R_2^{ASA}	R_2^{AS}	sun red, spotted	*arb*
R_2^{SO}		sun red, spotless	*arb*
R_2^{CS}	R^C	red calyx, spotted	*herb*
R_2^{DS}		thumbnail red, spotted	*arb*
R_2^{DO}	R_2^{EO}	thumbnail red, spotless	*herb.*
R_2^{FO}		green stem, spotless, tinged petal	*arb*
R_2^{GS}		weak thumbnail red, spotted	*arb*
R_2^{HO}		green stem spotless, petal untinged	*arb.*
R_2^{LO}	R_2^{O}	red leaf, spotless	Old World
R_2^{LS}	R^L	red leaf, spotted	*herb*
R_2^{LW}	R_2, S^W, S^C	*red leaf, spotted*	*barb purp*
R_2^{MS}		red margin, spotted	*arb*
R_2^{MO}	R_2^{NO}	red margin, spotless	*arb*
R_2^{OS}	r^g	green stem, ghost spot	*arb herb anom.*
R_2^{RS}	R	full red, spotted	*arb.* (*hirs*) (*barb*)
R_2^{TS}		green stem, tinged ghost spot	*arb*
R_2^{VS}		red vein, spotted	*arb*
R_2^{VO}	R_2^{WO}	red vein, spotless	*arb*
R_2^{GO}		gold petal spotless	*anom*
r_2^{OO}		*green, spotless*	*arb* (*herb*)
Rd		red dwarf	*hirs*
Rl_a		red lethal, complementary with factor(s) from Upland	*arb*
sh	s^h	short sympodia	*barb*)
Sr		spot reducer	*arb*
stg		female sterile	*hirs*
stg		female sterile	*herb*
stp		male sterile	Old World

GENE LIST FOR *Gossypium* (*Continued*)

Symbol suggested	Original symbol if different	Gene effect	Species
V_1	v_a	virescent a	*hirs*
v_1		virescent yellow	Old World
V_2	v_c	virescent c	*hirs*
v_2		virescent yellow	Old World
V_3	v_f	virescent f	*hirs*
v_3		virescent yellow	Old World
V_4	v v_k	virescent k	*hirs*
v_4		virescent yellow	Old World
V_5	v_l	virescent 1	*hirs*
cc		5 loculed bolls	*arb*
W_1	A	*Fusarium* resistance	*arb*, *herb*
W_2	B	*Fusarium* resistance	*arb*, *herb*
W_3	C	*Fusarium*-resist inhibitor	*arb*, *herb*
X		lint-color modifier	*arb*, *herb*
Y_1	Y^B	yellow corolla	*barb*
Y_1^p	y	cream corolla	New World
Y_2	Y^D	yellow corolla	*darwinii*
Y_a	Y	yellow petal	*arb*, *herb*
Y_a^p	Y_p	pale petal	Old World
y_a	y	white petal	Old World
Y_b		Chinese yellow petal	Old World
Y_b^p		Chinese pale petal	Old World
Y_c		yellow petal	*anom*
Y_c^p		pale petal	*anom*
Ydp		yellow depressor	*anom*

GENE LINKAGE IN *Gossypium*
ASIATIC COTTONS

Group	Linkage group and crossover value			
1 a	*L*	*cu*	*Lc*$_1$	
	—16.6—			*G. arboreum*
	—15	—19—		*G. arboreum*
	—28.7—			*G. arboreum*
	—29.9—			*G. arboreum*
	—27–32—			*G. arboreum*
	—21.5—			*G. arboreum* × *G. herbaceum*
b	*L*	*Li*$_4$	*Lc*$_1$	
	—17.1—	—20.5—		*G. arboreum* ×
	—26.9—			*G. herbaceum*
c	This chromosome carries a fuzz modifier			
2	*H*$_a$	*Lc*$_2$		
	—7.1—			*G. arboreum* × *G. herbaceum*
3	*Y*$_a$	*Lc*$_2$		
	—24—			*G. arboreum* × *G. herbaceum*
4	*P*$_s$	*Ve*		
	—16—			*G. arboreum*
	3 5 5 6 —			*G. arboreum* × *G. herbaceum*
5 a	*P*$_a$	*Ydp*		
	—29.7— interspecific			
b	*P*$_a$	modifiers of *Lc*$_1$		
6	*R*$_1$	*Y*$_b$		
	—1.2— interspecific			
7 a	*Chl*$_1$	*R*$_2$	*Cl*	
		—30—		*G. herbaceum*
	—9—			*G. arboreum*
b	*R*$_2$	wilt resistance		
c	*R*$_2$	*b*$_1$		
	—1.4—			
8	*Fz*	lint length, seed weight		
9	*h*$_b$	protruding stigma		
10	*Y*$_a$	petal length		

Gene Linkage in *Gossypium* (Continued)

NEW WORLD COTTONS

Group	Linkage group and crossover value			
1 a	R_1	·	cl_1	
	——13 9——			
	——16——			intraspecific
	—— 8 ——			interspecific
	——18 5——			
	——14 1–19 6——			
b	R_1	.		low lint index
2	R_2	:	cl_2	
	——10.4——			
3	H_1	:	chl_1	
4 a	H_2	:		short lint
b	H_2	.		lint color *G tomentosum* crosses
	H_2	:		nankeen lint
5 a	Cr	:		Lg
	——5——			
b	Lg	:		high wax content fineness (linear order not implied)
c	Cr	:	ck	
6	B_1	:	d_1	
7	B_2	:	B_3	
	——32——			interspecific
	——50——			intraspecific
8	Lc_1^M	:		shortened lint
9 a	V_1	:	Fgr	
b	V_1	:		green leaf

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Explanatory Notes

In the foregoing gene list, the symbolization adopted by Hutchinson and Silow, 1939 (*J. Heredity*, 30: 461–464), has been retained. Italicized symbols refer to genes from Old World species or to genes in New World species known to be located in the A genome. The use of parentheses in the last column indicates species to which the gene concerned has been transferred from its original species by hybridization.

COFFEE (*Coffea*)

About 60 species of the genus *Coffea* have been described. Most of these are found in Africa, especially in the Congo region, a few are native to



Figure 141. Model of a flowering and fruiting branch of Arabian coffee (*Coffea arabica*), reproduced from nature. (*Courtesy of Chicago Natural History Museum.*)

Asia, none to the Americas. All species so far studied have 11 pairs of chromosomes except *C. arabica* L., of Abyssinian origin, which has 22 pairs. This species was introduced into South America in 1718 and has become the chief crop plant of Brazil. Many varieties now exist, of which Typica is the most common. *C. arabica* probably arose through polyploidy, either through the crossing of two 22-chromosome species (amphidiploidy) or the doubling of the chromosomes of a single species

(autotetraploidy) This event must have taken place a long time ago since all genetic differences so far analyzed depend upon single pairs of genes and no mutants due to duplicate genes are known

Of the 20 mutant genes analyzed by Krug and Carvalho, 6 show essentially complete dominance, 7 are incompletely dominant, and 7 are recessive, in relation to the "normal type" All but 6 are classed as pleiotropic A number of cases of genic interactions are described in their 1951 paper, and other interesting facts on the genetics, reproduction, cytology, taxonomy, and economic importance of *Coffea* are discussed The paper is well illustrated with excellent drawings and photographs

Mendelian Characters in Coffee

Symbol	*Character*
ag[1]	angustifolia—narrow leaf, numerous stems from base
ag[2]	angustifolia—narrow leaf, one main stem
an	anomala—abnormal growth of various parts
Am	anormalis—abnormal growth—dominance incomplete
Br	bronze—young leaves bronze—dominance incomplete
C	calycanthema—petaloid calyx
Ct	caturra—plant shorter than Typica
ce	cera—yellow endosperm
Cr	crespa—crinkled leaves
Er	erecta—upright lateral branches, angle 25°
Fs	fasciata—fasciation—dominance incomplete
lr	laurina—small plant and leaves, seeds pointed below
Mg	maragogipe—gigas type
mo	mokka—small plant, smallest seeds known, domatia very large—dominance of *Mo* incomplete
na	nana—dwarf—*Na na*, murta, *Na Na*, bourbon (in presence of *tt*)
pr	purpurascens—purple leaves, pink flowers
sd	large sepals—well-developed persistent sepals—dominance of *Sd* incomplete
sf	semperflorens—continuous-flowering
T	Typica—primitive type—bourbon, *tt* (high-yielding)
xc	xanthocarpa—yellow-fruited—dominance of *Xc* incomplete

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The author is greatly indebted to Mr Krug and Mr. Carvalho, both of the Instituto Agronomico, Campinas, Sao Paulo, Brazil, for personally checking the foregoing facts on the genetics of coffee.

TOBACCO (*Nicotiana*)

The genus *Nicotiana*, a member of the nightshade family (Solanaceae), includes a large number of species and varieties. Most of the species are of New World origin There is also a large Australian group. The Indians

of the West Indies were raising tobacco when Columbus arrived there in 1492. Present domesticated types are varieties of *N. tabacum*, which has 24 pairs of chromosomes. Many species of *Nicotiana* have 12 pairs of chromosomes. *N. tabacum* is regarded as an amphidiploid resulting from the crossing of two of these.

Tobacco is naturally self-fertilized, but cross-pollination occurs also. Consequently an individual plant may well be heterozygous for numerous genes. Cultivated tobacco is highly variable, but relatively few spontaneous mutations have been observed to occur. The number of simple Mendelian differences identified so far is not great as compared with the numbers in cotton, barley, corn, or rice. Many of the differences in such characters as number and form of leaf, texture and commercial quality of leaf, and resistance to diseases and parasites are multifactorial. For the most part these have not been thoroughly analyzed.

As an example of the possibilities of applying breeding and selection to tobacco, East and Jones were able to produce to order a variety, Round Tip, that met certain leaf specifications laid down in advance as desirable for cigar wrappers. They did this by crossing two varieties, Broadleaf and Sumatra, chosen on the basis of their known genetic constitutions.

Mendelian Characters in Tobacco

Symbol	*Character*
a	auriculate
au	yellow stem
Br	brown seed
C	colored (with F, produces red pigment)
d	double flower
F	color factor (with c produces violet color, with C red)
I_1	intensifier of color, cumulative effect with I_2
I_2	intensifier of color, cumulative effect with I_1
L	long-petioled, l, short-petioled (epistatic over S)
ln	low nicotine content
m	mammoth (flowering restricted to short-day conditions)
mv_1	mosaic virus-resistant
mv_2	mosaic virus-resistant
P	pigment distribution inside the corolla
Pc	pigmented exterior surface of corolla
R	pigment extended deep into parenchyma of corolla
s	short-petioled, broadly sessile (epistatic over L)
Un	undulated leaf margin (incomplete dominance)
w	winged portion at base of leaf
wh	white-stemmed
Wr	wildfire resistance (resistant to bacterium *Pseudomonas tabaci*)
ws_1	purpurea white seedling } Both recessive genes ($ws_1\, ws_1\, ws_2\, ws_2$) required to produce white seedling. Ratio in F_2 from cross $ws_1\, ws_1 \times ws_2\, ws_2$: 15 green, 1 white
ws_2	chinchao white seedling }

Reference

East, E. M.: The Genetics of the Genus *Nicotiana*, *Bibliographia Genet.*, vol. 4, pp 213–320, 1928.

PROBLEMS

1. Which of the 10 plants described in this chapter are of New World origin?
2. Which of the 10 plants listed show polyploid chromosome series?
3. How do you account for the fact that man relies chiefly upon the grasses rather than upon other groups of plants for his food and the food of his domesticated animals? (All of the food plants described in this chapter except peas and tomatoes are classed as grasses.)
4. What are some of the factors that make the grasses favorable plants for genetic studies?
5. In which of the plants listed herein have geneticists identified genes for resistance against parasites?
6. What proportion of the genes for resistance in the 10 plants are dominant?
7. How many genes affecting flower color in peas are listed?
8. What color is expected from a cross between pinkish white (*am am*) and white (*a a*) in peas? Calculate the expected ratio in the F_2 from this cross.
9. Why is it so difficult to identify with certainty the wild ancestors of man's domesticated plants?
10. From the list of Mendelian characters in peas select those that you think represent the traits studied by Mendel, giving the linkage group for each, where known.

19

DOMESTICATED ANIMALS

In the introductory remarks to Chap. 18 on Domesticated Plants, certain general facts on domestication were pointed out. We shall now choose for discussion several domesticated animals, using as our guide in selection the economic importance, general popularity, and scientific interest of the species.



Figure 142. Choice long-horned cattle of the Ruanda-Urundi, East Africa The same type of cattle was found in Egypt 4,500 years ago. (*Courtesy of the Belgian Information Center, New York*)

A relatively small amount of precise genetic information has been published on the larger mammals There are two reasons for this scarcity of material: one is the long life cycle of the large mammals; the other is the

expense of their feed and care Practical breeding operations are usually not designed to answer fundamental problems in genetics With the smaller animals, such as mice and chickens, extensive lists of Mendelian characters are available

Let us begin with the species—or group of species—that is undoubtedly of greatest economic importance to man—cattle

CATTLE (*Bos taurus*)

Domesticated cattle are a product of the Old World According to Lush, the Egyptians began to use ox-drawn plows some time between



Figure 143. Zebu, Indian humped cattle, in Lincoln Park Zoological Gardens, Chicago (*Courtesy of Chicago Natural History Museum*)

5000 and 4000 B C Cattle, showing the characteristic hump of the zebu (*Bos indicus*), date back at least to 3000 B C in India A limestone relief[1] carved during the Fifth Dynasty in Egypt, about 2500 B C., and reused in the North Pyramid shows long-horned cattle which look exactly like those found today in Ruanda-Urundi in East Africa (Fig. 142).

Darwin thought that the many types of domesticated cattle in Europe, Asia, and Africa were descended from several wild species, including *B taurus* and *B indicus* (Fig 143) *The zebu and European cattle, however*, cross readily and produce fertile hybrids Several breeds, such as

[1] Picture in "Ancient Egyptian Animals," by Dorothy W. Phillips, Metropolitan Museum of Art, New York, 1948

the Afrikander of South Africa and the Santa Gertrudis of Texas (Fig 92), are in fact the product of crossing the zebu with European cattle. Since reproductive isolation (an important criterion of specific distinction in mammals) fails, some taxonomists class *B. taurus* and *B. indicus* as subspecies within a single species. According to Makino, the zebu and European cattle both have 30 pairs of chromosomes.

Cattle show great variability, and numerous characters have been identified as Mendelian. As usual in other animals, many of the differences in body conformation and physiology that are important in cattle breeding are multifactorial and not easily analyzed in Mendelian terms

Mendelian Characters in Cattle

Symbol	*Character*
a_1	achondroplasia-1—("bulldog"), lethal, *An*, very short legs (Dexter cattle)
a_2	achondroplasia-2—extreme type with short head, cleft palate, lethal
a_3	achondroplasia-3—variable in expression, usually lethal (Jerseys)
ag	agnathia—imperfect or missing jaws; limited to males
am	amputated—no legs, or legs only to elbows and hocks; lower jaw nearly absent, cleft palate, lethal (Holsteins)
an	ankylosis—lower jaw short and fused to skull, lethal (Norwegian Lyngdal cattle)
B	black—in hair, skin, hoofs, tongue, etc.
Br	brindle—black stripes on red or yellow (two factors), expressed only in *ee* animals
Bs	black spotting—expressed only in *ee* animals (Jerseys and Ayrshires)
c	albino—lack of color
ca	congenital cataract
D	dominant dilution—changes black to dun
De	double ear (Brahmans)
dr	dropsy—lethal (Swedish Lowland cattle)
e	red
ep	epitheliogenesis imperfecta—defective skin on lower legs and in mouth and nostrils, hairless patches (Holsteins and Jerseys)
fl	flexed pasterns
fu	fused teat (Herefords)
ha_1	hairlessness—lethal or sublethal (Holsteins and Jerseys)
ha_2	semihairlessness—thin, short, fine hair at birth, becoming coarse with age (Herefords)
ha_3	hypotrichosis with anodontia—at birth, completely hairless and toothless, fine hair later; sex-linked
ha_4	viable hypotrichosis—at birth largely hairless, except on extremities of legs and tail, eyelids, lips, inside ears, dewlap; teeth normal (Guernseys)
hy	hydrocephalus
i	recessive dilution (Jerseys and Guernseys)
Im	impacted molars—lethal during first week (Milking Shorthorns)
In	inguinal white
K	karakul—hair in tight curls (Ayrshire)
l	lameness—sublethal (Red Danish)

Symbol	Character
mu	muscle contracture—head bent back, joints stiff, lethal (Norwegian and Holstein cattle)
N	*NN* solid color, *Nn* roan, *nn* white, pigment in eyelashes and fringes of ears
no	notched ear
P	polled—*Pp* may have vestigial horns (scurs), more often in males
pa	parrot beak—similar to impacted molar
Po	three-toed (Holsteins)
po₁	polydactylism—extra toe on each front foot, limited to males, deleterious
P₃	black—pigmentation in muzzle, tongue, skin, etc
Re	red hair around eyes—modifier of S^H
S^C	color-sided (white dorsal line, white below, white feet)
S^D	Dutch-belted (alleles S^D, S^C, S^H, *S*, *s*, first four incompletely dominant over each other, but all four dominant over *s*)
S^H	Hereford pattern
S	Self color
s	white spotting (Holsteins, Guernseys, etc)
sh	short limbs—hoofs undeveloped, lethal (Swiss)
spa	spasms—normal at birth, lethal in a few weeks (Jerseys)
spi	short spine—lethal (Norwegian mountain cattle)
te	one left teat rudimentary (Guernseys)
Um	umbilical hernia
wn	recessive white (Indian cattle)
Wp	dominant white (English Park cattle)
wr	wry-tailed (Jerseys)

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HORSE (*Equus caballus*)

There is good evidence that the domesticated horse was derived from a wild species which formerly ranged from western Europe to eastern Asia *Several subspecies probably existed over this vast territory, just* as today there are several subspecies of the common zebra (*Equus quagga*) which extend from northern to southern Africa. Simpson is of the opinion that horses were first domesticated by men of Europe and Asia living about *2500* B C *He thinks that the process of capture and* training was done independently in different regions, by people classed as barbarians, and that by about 2000 B C domesticated horses had been adopted into the civilizations of China and Mesopotamia

The differences that existed among the various subspecies of the wild horse could in part account for the variability of domesticated horses; some of the variability, of course, resulted from selection and the crossing

of breeds following the initial domestication In Europe a type of wild horse known as the tarpan, perhaps the ancestor of the European horse, survived in certain places down to medieval times, while in Central Asia a similar wild horse, Przewalski's horse (*Equus caballus przewalski*), survived until very recent times, if not up to the present. It apparently mated freely with domesticated horses and produced fertile hybrids Its general body color is light yellowish or reddish gray; the mane, tail, and feet are black, with a black stripe down the back The distribution of the black pigment thus resembles that of the bay of the domesticated horse, which is regarded as possessing the wild-type pattern The horse has 33 pairs of chromosomes

Horses are less variable than some of the other domesticated animals This is perhaps due to their origin from a single wild species and to the limited uses for the horse With the exception of differences in color, relatively few clear-cut Mendelian characters have been described for the horse The many quantitative differences in size and body conformation are of course hereditary, but, as in other mammals, depend upon numerous genes and are not subject to analysis by ordinary pedigree methods

Mendelian Characters in the Horse

Symbol	*Character*
a	recessive black; *A*, bay (wild type, black mane, tail, feet, legs, reddish body)
b	brown
bl	bleeding (weakness of blood vessels in the nose)
D	dilution—dominance incomplete
E^d	dominant black
E	wild type (restriction of red to body, mane and tail dark)
e	red (sorrel); extension of red including feet, mane, tail
G	gray (black or very dark at birth, becoming lighter with age, epistatic to other colors)
m	white markings on face and feet (blaze or forehead star and stockings, variable in expression)
P	piebald (extensive white spotting as in Pinto or calico ponies)
R	roan (white hairs scattered among colored, giving red roan or blue roan)
Ro	roaring (breathing defect due to paralysis of muscles that open larynx)
S	silver dapple [black reduced to dark cream, mane and tail white or silver (Shetlands), red moderately reduced]
T	trotting gait, *t*, pacing gait
W	dominant white, eyes brown or blue, skin largely pink, epistatic over other colors

(Castle assumes that all horses have a color factor *C*, corresponding to gene *C* in guinea pigs and other mammals; but he lists no mutant allele of *C*.)

Combinations with *dd*

A- B- dd E-	wild type and ordinary bay
aa B- dd E-	black
A- bb dd E-	chestnut

Symbol	Character
aa bb dd E–	brown (liver)
A– (or aa) bb dd ee	sorrel
	COMBINATIONS WITH DILUTION FACTOR, *D*
A– B– Dd E–	buckskin ("dun"), coat yellowish, mane and tail black, eyes dark
A– bb Dd E– / *A– bb Dd ee*	*Palomino, coat golden yellow, mane and tail whitish, eyes dark*
aa B– Dd E–	Mouse, coat, mane, and tail dilute black ("brown"), no light points, eyes dark
A– B– DD E–	albino, type B, coat cream, cinnamon buff (Ridgeway), mane dilute black, eyes blue
A– bb DD E–	albino, type A, coat ivory, mane white, skin pink, eyes blue

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PIG (*Sus scrofa*)

The domesticated pig of Europe, which is the chief source of the swine of the New World, was derived from the European wild boar (*Sus scrofa*, Fig. 144), a species that is still extant. The two cross and produce fertile hybrids. Many breeds of pigs have been produced, largely as the result of selection, aided by occasional crossing between breeds. Close inbreeding is usually avoided today. The breeds differ in color and color pattern, size, conformation of body, shape of skull and jaws, length of legs, etc.

The hair color of the wild boar is dull black, with the individual hairs banded in pale yellow (agouti pattern). The agouti bands are wider on the ventral surface. Consequently, like most wild mammals, the wild boar is lighter in color underneath. There is no distinct spotting. The ears are pointed and erect. In contrast with domesticated pigs the body is slender, the legs are rather long, the shoulders are strongly developed, and the hams are weak. It is therefore much poorer as a meat animal for human consumption than the domesticated pig.

Economically important characters, such as size, rate of growth, body proportions, quality of meat, and temperament are multifactorial. Their mode of inheritance has not been fully analyzed. The list of demonstrated Mendelian differences is not a long one in swine. Smith et al. state that in the mating of pigs of different breeds it is not possible to predict with any

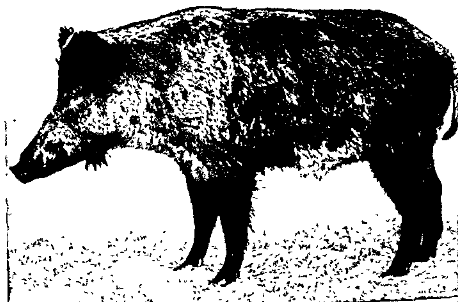


Figure 144. Wild boar of Europe (*Sus scrofa*). (*Courtesy of Chicago Natural History Museum*)

high degree of certainty the color of the offspring, unless the mating has been made before. They point out that the genotype governing the same phenotype varies radically from breed to breed and even within a breed All breeds of pigs so far examined have 20 pairs of chromosomes.

Mendelian Characters in the Pig

Symbol	*Character*
A	agouti—individual hairs banded (wild type, not found in domesticated pig)
Be	belted—white band around forequarters as in Hampshire
br	Berkshire-type dished face
cp	cleft palate and split ear
cr	cryptorchidism
Cu	curly hair
d	defective skull
e	red; e^p, black spotted; *E*, black
Ea	erect ear, dominance may be incomplete
fe	fecundity, *Fe*, wild litter size (4)
h	hydrocephalus, lethal
ha	hairless
hc	half color—anterior half of pig white
he	hemophilia, autosomal
Hl	harelip
hr	hernia
Hw	hair whorls

Symbol	Character
hy	hydrocephalus
I	inhibitor of color, as in Yorkshire; i^d, dilution (blue-roan), *i*, intense color
k	kinky tail—fusion of vertebrae
p	paralysis of hind limbs
r	red eye, black in coat reduced to light sepia
s	white spotting
sa_1	sandy } both genes together when homozygous give white
sa_2	sandy }
Sn	syndactyly (mule foot)
sr	short rump
w	recessive white
wa	wattles
Wo	woolly hair

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SHEEP (*Ovis*)

Sheep were among the first animals to be domesticated. A large number of wild species of *Ovis* as well as domesticated breeds exist today. It is uncertain whether the many breeds all trace back to a single wild ancestral species or to several Makino reports 27 pairs of chromosomes in sheep, with no racial difference

Fewer Mendelian characters have been demonstrated in sheep than in most domesticated animals. The most important characters, the amount and quality of the wool and the meat, depend largely upon multiple genes, these have not been thoroughly analyzed

Mendelian Characters in Sheep

Symbol	Character
A^b	dominant black as in Karakul (black changing to gray except on extremities)
an	ancon (Otter), a type of achondroplasia
b	brown, chocolate color
Be	bent-tail, S-shaped tail as in Karakul, *Be be*, intermediate
Dr	drooping ear, *Dr dr*, intermediate
e	red wool
ea	earless, *Ea Ea*, long ear, *Ea ea*, short ear
F	white fat; *f*, yellow fat

Symbol	*Character*
G	gray, *GG*, lethal
K	Karakul, wool in tight ringlets, in some breeds incomplete dominance
N	extra nipples—multiple factors
P	polled, horns recessive in females, dominant in males [Some breeds are *PP*, some *pp*, in some breeds (Dorset Horn, Lonk) both sexes are horned; in Merino, males are horned, females hornless; in some breeds both sexes are hornless (Down, Lincoln, Cotswold, Leister)]
pr	convex profile
s	spotting, black over eyes, on nose, lips, and legs (Gromet, or badger face)
s^p	piebald, as in Spanish sheep, $S^p s^p$, white patch on head, tail partly white
Sh	short tail
W	dominant white

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DOG (*Canis familiaris*)

In his comprehensive work on "The Variation of Animals and Plants under Domestication," published in 1868, Charles Darwin devoted thirty pages to the origin and history of the dog. He came to the conclusion that domesticated dogs were derived from several wild species. He noted that nearly all living tribes of men all around the world were the owners of dogs and that in each geographical region the dogs resembled closely in structure and behavior the wild species of Canidae (wolves and jackals) native to the region.

Archeological research has shown that the dog was domesticated long before historic times. Bones of dogs are found with those of cave man in Europe. It seems probable that the dog was the first animal to be truly domesticated by man and that this symbiotic relationship originated during the immensely long stretch of time that man got his living by hunting and food gathering, before the invention of agriculture. The domestication of the dog was most natural, since the ancestors of the dog were also hunters, as well as social animals. They had the temperamental aptitude that made them amenable to the discipline of human association and were not large and strong enough to be dangerous to the early hunters and their families. Among some of the nomadic tribes still living in the hunting and food-gathering stage, for example, the Bushmen of South Africa, the Aborigines of Australia, and the Eskimos of the arctic region, the dog is the only domesticated animal. Apparently, various wild species of wolves and jackals are capable of crossing with each other and with

dogs and of producing fertile hybrids On his longest migrations on foot or by boat or raft man probably took along his dogs Hybridization was thus made possible with the dogs of other tribes or with wild Canidae, this favored the increasing variability of the dog and may in part explain the fact that the dog is the most variable of domesticated animals In later times, with the development of agricultural civilizations, there

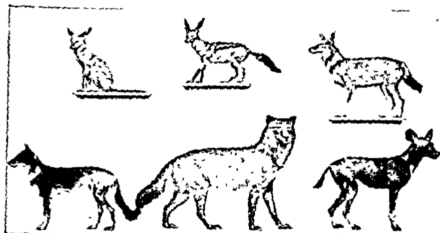


Figure 145 Members of the dog family (Canidae) *Top row, left to right* North African jackal (*Thos aureus*), Black-backed jackal (*Thos mesomelas*); Abyssinian wolf (*Canis simensis*) *Bottom row, left to right* Dhole (*Cuon dukhunensis*) from India; Alaska wolf (*Canis lupus*), African hunting dog (*Lycaon pictus*) from Abyssinia. (*Courtesy of Chicago Natural History Museum*)

was a preservation of a great variety of mutants and the selection of different types to satisfy the many uses that man found for the dog The ancient Assyrians and Egyptians had distinct breeds of dogs

Mendelian Characters in the Dog

Pigmentation

The melanin pigment in the skin, hair, and eyes of dogs is essentially like that in other mammals Several series of alleles affect its development, just as in the guinea pig, described in Chap 6 In details, however, there are many differences, as one would expect in widely separated orders of mammals Some of the conclusions embodied in the table below rest upon facts reported by fanciers engaged in developing special breeds and have not been subjected to the same rigorous tests as in the case of the laboratory rodents Pigmentation in the dog is highly complex and variable—due to the probable diverse origin of the dog and to its worldwide domestication over many thousands of years Opportunities for the

accumulation of many mutations have been ideal. Investigators of dog genetics are not in agreement on all points. The list of genes and allelic series given below may be modified in some details as further facts accumulate. The dog has a very large number of chromosomes—39 pairs.

Symbol	*Character*
	AGOUTI SERIES OF ALLELES
A	dominant black
a^y	dominant yellow (tan)
a^w	agouti (wolf gray, wild type)
a^t	black and tan, with restricted tan markings on feet and muzzle
b	chocolate-colored hair, skin, eyes, B, black
Bl	black tongue (Chows), $Bl\ bl$, intermediate, $bl\ bl$, pink tongue
	ALBINO SERIES OF ALLELES
C	intense pigmentation
c^{ch}	intensity reduced, red reduced to yellow (Chinchilla)
c^d	white hair, dark skin and eyes, as in Poodles and Alsatians
c^b	pale-gray hair, pale-blue eyes appearing red in certain light
c	albino—pink nose, blue eyes, white hair
d	dilution—hair "blue" as in Greyhound, eyes and skin dilute
	EXTENSION SERIES OF ALLELES
E	dominant black
e^{br}	brindle, as in Great Dane and Boxer
e^m	yellow (fawn), with black mask on yellow
e	red or yellow (fawn) without black mask—ee is epistatic to black resulting from genes in other series
H	harlequin, Hh, many spots on white or gray field; HH, white with small gray spots—pups weak, deaf, eyes small and defective (Great Dane, Dachshund, Dunkerhound)
	EYE-COLOR SERIES OF ALLELES
Ir	iris dark
Ir^m	medium (hazel)
ir^y	light yellow, dominance probably incomplete
p	pink-eyed dilution
Ro	roan or ticking (dark hairs scattered among white)
ru	ruby eye—red light reflected from eye in darkness, instead of yellowish green
s	white spotting; ss, large irregular white spots, Ss, some white on chest, paws, or head
W	dominant white hair, skin, nose, eyes pigmented

Characters Other Than Pigmentation

Many characters involving the anatomy, physiology, and behavior of dogs are known to be hereditary. In the majority of cases, however, the

precise Mendelian mechanism is undetermined This is especially true for sensory and behavioral differences, as displayed in hunting and herding dogs. Many anatomical, physiological, and behavioral traits apparently depend upon multiple factors, hence their analysis is difficult Many such traits are discussed by the authors cited below

Symbol	*Character*
Ca	cataract
ch	coarse hair
cp	cleft palate (Bulldog)
Dc	dewclaw (1st digit present on hind foot), in some breeds recessive
Dt	docked tail, in some breeds *Dt Dt*, lethal
	EAR-CARRIAGE ALLELES
Ea	semi-erect ear (Terrier)
Ea^1	lop-eared (Hounds)
ea	erect ear, Ea^1 *ea*, intermediate
he	hemophilia (sex-linked)
Hy	hypotrichosis (hairless)
Kt	kinky tail (Bulldog)
oj	overshot upper jaw (Dachshund)
Pe	pendant ears
Pn	pointed nose
r^a	retinal atrophy (Irish Red Setter)
Se	small ear (Alsatian), *se*, large ear (Pointer)
Sh	short hair
Sl	short legs (achondroplasia), *Sl sl*, intermediate
sn	snub nose (Pekingese, Bulldog)
St	straight hair, *St st*, wavy, *st st*, curly
Tf	tail feathering
Te	triangular ears
um	umbilical hernia
ur	high uric acid excretion, with tendency to kidney stones (Dalmatian)
Wi	wire hair

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CAT (*Felis libyca*)

The common domesticated cat of Europe and the United States, sometimes called *Felis domestica*, probably originated through the domestication of the wildcat *F. libyca* (Fig 146), which ranges in Africa from the region north of the Sahara to the southern tip of the continent.

The wild species is larger than the domestic cat. Austin Roberts cites measurements for *F. libyca* showing the following means: head and body length, males 559 mm., females 527 mm.; cranial length, males 101 5 mm , females 96.2 mm.; brain-case width, males 47.8 mm., females 47.2 mm.; zygomatic width, males 73.9 mm., females 69.1 mm.



Figure 146. Wildcat of Africa (*Felis libyca*), supposed ancestor of the domesticated cat of Egypt. (*Courtesy of Chicago Natural History Museum*)

In color *F. libyca* resembles the tabby. In the tabby, the long guard hairs are black-tipped, with one or more subterminal bands of yellowish (agouti banding); on the sides of the body dark and light dorsoventral stripes alternate. A dark stripe runs along the center of the back In the black stripes some of the guard hairs are solid black and others have unusually long black tips.

The wild species varies considerably throughout its extensive range, and a number of subspecies have been described. *F. libyca* crosses readily with domestic cats, and according to J. Stevenson-Hamilton, late warden of Kruger National Park, South Africa, a hybrid (male) that he observed was fertile. He states that during Pleistocene times and more recently

the range of *F. libyca* included a large portion of Europe Some authors consider the European wildcat, still present in certain forested mountain areas, as constituting a distinct species, *F. catus*. In color it also resembles the domestic tabby and crosses with domestic cats

The ancient Egyptians were probably among the first to domesticate the cat Statues of cats dating as far back as the Twelfth Dynasty (1991–1778 B C.) have been found Paintings in tombs of the Eighteenth Dynasty, about 1400 B C, show cats with the typical tiger pattern

In Asia other species of *Felis* are found; from these some of the domesticated cats in that continent may be derived The Siamese cat is thought to have an origin distinct from common cats

The lack of anatomical variability in the domesticated cat is remarkable in comparison with the extreme variability of the dog. The explanation for this difference is not obvious. It may be due in part to the diverse origin of the dog. The cat has 38 pairs of chromosomes

Mendelian Characters in the Cat

Symbol	*Character*
A	dominant black (of Siamese)
a^w	agouti pattern (tabby, wild type)
a	non-agouti—hairs without subterminal bands
C	intense color
c^k	chinchilla—pigment reduced
c^b	Burmese pattern—born white, blackish pigment developing later on face, ears, feet, tail, coat dusky, eyes yellowish
c^s	Siamese pattern—born white, similar to Burmese, but greater reduction of pigment; eyes blue
d	Maltese—black diluted to bluish gray, yellow diluted to cream
e	yellow, E, black, Ee, tortoise-shell (black-and-yellow spotted), sex-linked
l	long hair (Angora)
P	polydactyly
s	white-spotted, dominance of S (self) incomplete
T	tailless, t, long tail, Tt, bobtail
W	dominant white—epistatic to other color genes, eyes either yellow or blue, if blue, deaf, if blue on one side only, deafness limited to same side

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Stevenson-Hamilton, J. "Wild Life in South Africa," Cassell & Co, Ltd, London, 1950.

MOUSE (*Mus musculus*)

The house mouse is of Asiatic origin Several subspecies exist in Asia and Europe The common house mouse (*Mus musculus domesticus*) has followed man in his migrations and is now to be found in every continent, living as a commensal in and around human habitations This relationship has probably endured for many thousands of years, perhaps from the beginning of agriculture with the storage of grain. Mice were abundant in ancient Egypt The Egyptian's veneration of the cat was perhaps due to its value as a check on mice

The Chinese were among the first to breed the mouse. White mice and spotted mice were known in China as early as 1100 B.C. White mice are mentioned by Aristotle. Fancy varieties were kept in Europe during the nineteenth century, and the mouse served as the first mammal in which Mendelism was demonstrated, in 1902 The list of known Mendelian characters has grown at an accelerated pace during the past fifty years. As a result we have more detailed knowledge about the genetics of the mouse than of any other mammal unless it be of man himself. There are 20 pairs of chromosomes in the mouse.

Mendelian Characters in the Mouse[1]

(Linkage groups indicated by Roman numerals, genes in group XX are sex-linked)

Symbol		*Character*
A	V	gray-bellied agouti
a	V	non-agouti
a^{t}	V	black-and-tan
A^{w}	V	white-bellied agouti
A^{y}	V	yellow
ac		absence of corpus callosum
**ag*		agitans
Al		alopecia
an	VIII	anemia
**ax*		ataxia
b	VIII	brown
**Bn*	XX	bent tail
**bp*	V	brachypody
**Br*	XX	brindled
bt	VI	belted
c	I	albinism
c^{ch}	I	chinchilla
c^{e}	I	extreme dilution
c^{i}	I	intense chinchilla
c^{m}	I	superalbino
Ca	VI	caracul
**Cd*		crooked

[1] From Gruneberg.

Symbol		Character
ch		congenital hydrocephalus
cr		crinkled
**ct*		curly tail
d	II	Maltese (blue) dilution
*d^l	II	dilute lethal
**dr*		dreher
du		ducky
dw		pituitary dwarfism
ey-1, *ey-2*		anophthalmia
f		siderocyte anemia (flexed tail, belly spot)
fi	V	fidget
**fr*	I	frizzy
Fu	IX	fused
fz	XIII	fuzzy
gl		gray lethal
hj		hypotrichosis juvenilis
**Hk*		hook
hr	III	hypotrichosis cystica (hairless)
*hr^{ba}	III	hypotrichosis cystica (bald)
hr^{rh}	III	hypotrichosis cystica (rhino)
hy-1	V	hydrocephalus-1
hy-2		hydrocephalus-2
hy-3		hydrocephalus-3
ic		ichthyosis
i		otocephaly
je	XII	jerker
ji	X	jittery
Ki	IX	kinky tail
kr	V	kreisler
ln	XIII	leaden
Lp		loop tail
lr		lens rupture
Lt	VIII	light
lx	III	hemimelia tibiae (luxate)
m	VIII	misty
mi	XI	microphthalmia
**Mo*	XX	mottled
my		myelencephalic blebs
N	VI	hypotrichosis hypokeratotica (naked)
o	I	oligodactylism
**ob*		obese
p	I	pink-eyed dilution
p^r	I	ruby
pa	V	pallid
pg		pygmy
pi	III	pirouette
**pt*	VIII	pin-tailed
py	XIII	polydactylism
r	IV	rodless retina

Symbol		Character
Re	VII	rex
rl		reeler
**ro*	V	rough
ru	XII	ruby eye
s	III	piebald
sb		stub
sc		screw tail
Sd	V	Danforth's short-tail
se	II	short ear
sh-1	I	shaker-1
sh-2	VII	shaker-2
si	IV	silver
Sp	XIII	splotch
st		shaker short
sy		shaker with syndactylism
T	IX	brachyury
t^0, t^1, t^2–t^{10}	IX	anury
**Ta*	XX	tabby
te		light head
**tp*	I	taupe
Tr		trembler
**Ts*		tail short
U		umbrous
un	V	undulated
ur		urorectocaudal syndrome
v	X	Japanese waltzer
Va		varitint waddler
**vt*	VII	vestigial
W	III	dominant spotting (macrocytic anemia)
W^v	III	dominant spotting (viable allele)
wa-1	XI	waved-1
wa-2	VII	waved-2
**wb*		wabbly
Wh	XI	white
wl		wabbler lethal

The symbols in the above list are those recommended by the committee on mouse genetics nomenclature (Dunn, Gruneberg, and Snell, *J. Heredity*, 31:505-506, 1940) or symbols introduced later in conformity with the suggestions of that committee Dr Grüneberg suggests that it would be very desirable in the interest of uniformity if future authors would conform to those recommendations

In addition to the genes shown in the list above, there are the histocompatibility genes (or antigens) with symbols *H*-1, *H*-2, *H*-3, etc.

The author is especially indebted to Dr Grüneberg for supplying a supplementary list of genes (indicated by *) published since the publication of his book "The Genetics of the Mouse."

Reference

Grüneberg, Hans: "The Genetics of the Mouse," 2d ed , Martinus Nijhoff, The Hague, 1952. (1,751 titles are listed in the bibliography of this book)

FOWL (*Gallus*)

The common fowl, or chicken, is an Oriental bird The date of its first domestication probably came long after that of the dog and some time following the domestication of the horse. A settled agricultural way of

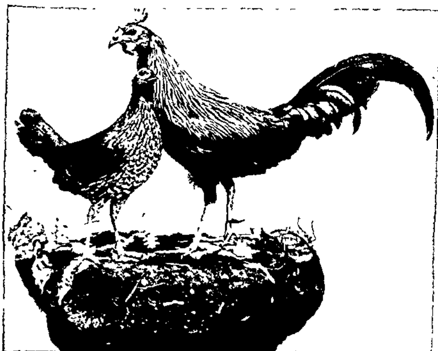


Figure 147. Red jungle fowl (*Gallus gallus*) of southern Asia, a probable ancestor of the domesticated fowl. (*Courtesy of Chicago Natural History Museum.*)

life rather than a nomadic existence is essential for the breeding of such a bird

In the Old Testament (King James version) the word *fowls* is used for birds in general But there is no reference to the domesticated fowl; there is a reference to a crowing cock in the New Testament. According to Darwin, in his book "The Variation of Animals and Plants under Domestication," the fowl is not figured on the ancient Egyptian monuments, nor is it mentioned by Homer and Hesiod (about 900 B C), but is referred

to by Theognis and Aristophanes between 400 and 500 B.C. Darwin concluded that the domesticated fowl apparently reached Europe about the sixth century B.C. Ancient writings indicate its domestication in India and China some centuries earlier It was found in Britain by Julius Caesar.

The genus *Gallus* consists of several species of wild jungle fowls which together have a wide range stretching from India in the west through Burma, Thailand, Malaya, Indo-China, and Indonesia to the Philippines The members of this genus are characterized by a stout and slightly curved bill, strong straight toes adapted for running and scratching, and fleshy head furnishings consisting of comb, wattles, and ear lobes

Darwin regarded the red jungle fowl *G. bankiva* (*G. gallus*, Fig 147), which is the most widely dispersed species of *Gallus*, as the probable ancestor of the domesticated fowl In plumage this species resembles the breed known as the Brown Leghorn. The voice of the red jungle fowl resembles that of the domesticated fowl. Hutt gives it as his opinion that three other species of *Gallus* may have contributed to the ancestry of the fowl He states that hybrids between any species of *Gallus* and the common fowl are fertile.

The name *G. domesticus* is frequently applied to the fowl This implies specific distinction, which is questionable zoologically, although the name is unobjectionable as a descriptive term. Many investigators have studied the chromosomes of the fowl. Owing to the many small chromosomes, counts are difficult The most recent reports indicate that there are 38 pairs of autosomes and two X chromosomes in the male, 38 pairs of autosomes and one X chromosome in the female. As in other birds, the female is the heterogametic sex.

Taken together, the domesticated fowls all over the world show a high degree of variability in size, body proportions, color and structure of plumage, head furnishings, and other characters How much of this variability is due to the diverse origin of the fowl and how much to man's preservation of mutations is unknown. For a number of reasons the fowl is a favorable animal for genetic experiments. Many Mendelian traits have been described The following list follows Professor Hutt's excellent book, cited at the end of the section.

Mendelian Characters in the Fowl[1]

Symbol	*Character*
a	albinism, autosomal—lack of melanin
ab	barring, autosomal (as in Hamburgs and Campines)
al	albinism, sex-linked—reduction in melanin
Ap	apterylosis—reduction in feather tracts, semilethal
B	barring, sex-linked (as in Plymouth Rocks)
bd	breda comb— ♀'s, combless; ♂'s, two small papillae as comb

[1] After Hutt.

Symbol	*Character*
Bl	blue; *Bl Bl*, black; *Bl bl*, blue, *bl bl*, blue-splashed white
Br	brown eye—color from yellow-orange to bay, sex-linked
By	brachydactyly shortened outer toe, *By by*, intermediate
c	recessive white—as in Plymouth Rocks and Dorkings
ch	chondrodystrophy—lethal
Cl	cornish lethal—*Cl cl*, short legs, *Cl Cl*, lethal
cn	crooked-neck dwarf, lethal before hatching
Cp	creeper—shortened and malformed legs, *Cp Cp*, lethal
Cr	crest
D	duplex comb
dp	diplopodia—usually six toes in two sets of three each
dw	dwarf—weight of adults reduced 30% in ♀'s, 42% in ♂'s, fertile, sex-linked
e	Columbian restriction (melanin reduced, as in light Brahmas)
F	frizzling—rachis and barbs much curled
Fl	*flightless—shafts of flight feathers break off*
fr	fray—defective barbules
g	yellow head—skin of comb, face, and wattles remain yellow
h	silkiness (hookless), barbules lack hooks
Hf	hen feathering—effect limited to males
I	dominant white—inhibition of black, as in white Leghorns
id	dermal melanin, dominance incomplete, sex-linked
ig	cream (inhibitor of gold)
j	jittery—nervous disorder, head retracted over back, sex-linked lethal
K	slow feathering, sex-linked
ko	head streak—dark head streak, sex-linked
l	recessive lethal white
la	lacing—feathers bordered by black
Li	light down (inhibitor of brown), sex-linked
lo	congenital loco—lethal a few days after hatching
M	multiple spurs
ma	marbling—irregular striping in down
Mb	muffs and beard—elongation of feathers at sides of face and under lower beak, *Mb mb*, intermediate
md	missing mandible—lethal
mf	modified frizzling—reduces frizzling
mi	microphthalmia—bilateral, eyes about half normal size, blind
mo	mottling—black eliminated from feather tips
mx	amaxilla—maxillae absent or much reduced, lethal
n	naked—sex-linked semilethal, deficient feathers more extreme in ♀'s
Na	naked neck—feathers lacking on neck
O	blue egg—blue pigment throughout shell; in South American varieties
P	pea comb
pi	pied—mixture of black and white plumage
pk	pink eye—eye pink, plumage of colored birds, blue
{ *Po*	polydactyly—duplicated hallux, irregular expression
{ Po^d	*duplicate*—extreme duplication of hallux
{ *po*	normal toes
R	rose comb
re	red eye—feather pigmentation reduced
Rp	*rumplessness*
rp-2	recessive rumplessness ("roachback"); low penetrance

Symbol	*Character*
rs	red-splashed white—melanin restricted
S	silver (*s*, gold), sex-linked
Sd	sex-linked dilution
sh	shaker—nervous disorder: rapid vibration of head and neck; affected usually die before sexual maturity; sex-linked
sl	spurless
sm	short mandible, semilethal
sn	sunsuit—remiges and retrices reduced in number and length; beak and toenails distorted
Sp	spangling—feathers with black tips, incomplete dominance
st	unstriped
sy	stickiness—abnormal embryos; lethal before hatching
su	short upper beak; semilethal
sw	snow white—down white instead of cream, yellow, or greenish
T	normal (rapid) feathering
t^s	retarded feathering
t	tardy feathering
ta	talpid—wings with several digits, short and palmate, lethal
td	thyrogenous dwarfism—multiple abnormalities
U	uropygial (*UU*, oil gland missing; *Uu*, bifurcated papilla)
v	vulture hocks—feathers on tibia large and stiff
W	white skin
wg	wingless, lethal
zl	lethal some time after hatching; sex-linked

Linkage in the Fowl

Since there are about 40 pairs of chromosomes in the fowl, the locating of genes on a particular chromosome is a slow process. The relatively large number already located on the X chromosome is due in part to the ease of discovery of sex linkage. The X chromosome, however, ranks fifth in size and ought therefore to carry a larger proportion of the genes than most of the other chromosomes.

Chromosome Maps of the Fowl

(Numbers indicate crossover percentages between successive genes)

SEX-LINKED

Symbol		*Character*
ko		head streak
	13	
sd		dilute
	?	
B		barred
	10	
Id		inhibitor of dermal melanin
	27	
Br		brown eye
	10	
Li		light down
	16	
S		silver
	5.5	
dw		dwarf
	5.5	
K		slow feathering

Location on X chromosome unknown: *al*, albino; *j*, jittery, *n*, naked, *sh*, shaker, *zl*, lethal

Symbol		*Character*
		LINKAGE GROUP 2
Cp	0 4	creeper
R	30	rose comb
U		uropygial
		LINKAGE GROUP 3
Cr	12 5	crest
I	17	dominant white
F		frizzled
		LINKAGE GROUP 4
O	5	blue egg
P	33	pea comb
ma	46	marbling
Na		naked neck
		LINKAGE GROUP 5
D	28	duplex comb
M	33	multiple spurs
Po[d]		duplicate
Po		polydactyly
		LINKAGE GROUP 6
h	12	silkiness
Fl		flightless

Reference

Hutt, F. B "Genetics of the Fowl," McGraw-Hill Book Company, Inc , New York, 1949

PIGEON (*Columba livia*)

Pigeons were domesticated many centuries ago Their source is the wild species known as the rock dove (*C livia*) of the Old World (Fig 148) The color of the rock dove, which may be regarded as the wild type of the pigeon, is slate blue, somewhat lighter on the wings. Across the wings extend two transverse black bars The rump is whitish, as can be distinctly seen as the bird takes flight, neck and breast, iridescent green and purple; primary wing feathers and tail feathers, dark-tipped; outer tail feathers, white on the outer web The iris of the eye is orange, the feet are unfeathered and red, and the bill is black.

The male pigeon has 39 pairs of autosomes and two X chromosomes; the female has 39 pairs of autosomes and one X chromosome A very large number of varieties and breeds have been developed through selection of mutations that have occurred from time to time, combined with crossing Many investigators have contributed to our knowledge of the genetics of the pigeon A comprehensive and valuable work on the pigeon by Levi contains a chapter summarizing this knowledge, to which the

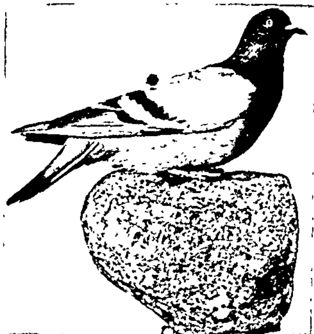


Figure 148. Wild rock dove (*Columba liria*) of Europe and Asia, supposed ancestor of the domesticated pigeon (*Courtesy of Chicago Natural History Museum*)

reader is referred for more detailed descriptions and for a bibliography on the pigeon.

Mendelian Characters in Pigeons

Symbol	*Character*
at	ataxia—ataxic behavior, brain, especially cerebellum, of inferior size
b	chocolate—skin, beak, and claws pale, feathers tawny with brown pattern; adult iris lacks most yellow color, sex-linked
B^A	ash red—feathers chestnut and gray; skin, beak, claws, somewhat depigmented, sex-linked
B^{Ol}	faded—slight reduction of pigment in plumage; homozygote nearly white, sex-linked
B^{St}	almond—reduction of pigment in skin, claws, beak, feathers; homozygote nearly white; sex-linked
C	blue checker
c	barless
cl	clumsy—apparently defective vision
cr	crest—feather whorl on back of head
C^T	T pattern—black, blue tail or black check
d	dilution (silver)—reduction in pigment in skin, beak, claws, retina, plumage tawny with dun pattern; sex-linked
d^P	pale—reduction in pigment, intermediate between dilution and wild type, sex-linked

Symbol	Character
e	red—beak, claws, skin, light, feathers chestnut red
G	grizzle—finely stippled decoloration, dominance incomplete
gr	grouse—tarsi and toes feathered, *Gr gr*, feathers usually on tarsi
In	indigo—reduction in pigmentation tending to reddishness, *In In*, more pronounced
L	lace or silky—barbules weak, barbs tend to curl; *LL*, more pronounced
My	milky—reduction in pigmentation, with little reddish
n	glandless—absence of oil glands of tail
na	nakedness (featherless)
o	opal—reduction of pigmentation in feathers, skin, beak, and claws
Od	dominant opal—similar to opal, except less reddish
p	porcupine—feathers fail, more or less, to expand from sheath
py	polydactyly—one or two extra toes on inner tarsus, usually extra pollex; projecting lower bill, lethal before maturity
sy	smoky
S	solid color (black)
tr	pearl eye—iris white
w	webfoot—variable webs between toes

Reference

Levi, Wendell Mitchell: "The Pigeon," R. L. Bryan Co., Columbia, S.C., 1941

PROBLEMS

1. What is the continent of origin of each of the nine domesticated animals described in this chapter?

2. Why do some taxonomists regard East Indian humped cattle and European cattle as members of a single species?

3. Why is it impossible to obtain a pure-breeding race of Palomino horses? What color variety in cattle offers the same difficulty?

4. In the pig, two genes are listed that reduce black to "sandy." A cross between these two produces black. Animals homozygous for both sandy genes are white. Calculate the F_2 phenotypic ratio from a cross between the two types of sandy.

5. How do you account for the great diversity in the domesticated dog compared to the small amount of variability in the cat?

6. What are the reasons for thinking that the dog was the first animal domesticated by man?

7. What are the factors that make mice and chickens especially favorable animals for genetic investigations?

8. How many of the 20 chromosomes in the mouse are known to carry genes?

9. What percentage of the mutations in mice are dominant?

10. What are some of the reasons for the overwhelming popularity of the fowl as a domesticated bird?

APPENDIX A

MENDEL'S AUTOBIOGRAPHY

Worshipful Imperial-Royal Examination-Commission [1]

In accordance with the exalted regulations of the Ministry for Ecclesiastical Affairs and Education the respectful undersigned submits a brief sketch of his life.

He was born in 1822 in Heinzendorf in Silesia where his father owned a small farm (See Enclosure A) After having attended the elementary school of his village and subsequently the Piarist College [Piaristen-Collegium] in Leipnik, he was admitted in 1834 to the first Grammar class of the Imperial-Royal Gymnasium of Troppau. Four years later several incidents of misfortune which followed each other in quick succession made it completely impossible for his parents to pay for the expenses connected with the studies, and the respectful undersigned, who at that time was only 16 years old, found himself in the deplorable situation of having to earn his own support He, therefore, attended the courses for "teacher candidates and private tutors" at the District Main School [Kreis-Hauptschule] in Troppau and since he was highly recommended in the certificate of aptitude which attested his passing the examination, he succeeded during his humanistic studies to earn by private tutoring an amount sufficiently large to permit a very modest way of living (Enclosure B)

In 1840 after having completed his studies at the Gymnasium his first concern was to secure the means necessary for continuing his studies In Olmütz he attempted therefore repeatedly to offer his services as a private tutor, but on account of the lack of friends and of recommendations his efforts remained unsuccessful The grief resulting from these shattered hopes and the uneasy and sad prospects for the future were of such a deep impact that he fell ill and had to spend a whole year with his parents to recuperate

Finally, in the following year the respectful undersigned was in the desired position to give lessons in Olmütz and at least to cover his most urgent needs while continuing his studies Applying himself to his fullest capacities he succeeded in completing the two years of philosophical studies (Enclosures D, E, F, G) The respectful undersigned felt that it was impossible for him to continue to expend such efforts, and after the completion of his philosophical studies he felt therefore compelled to enter a profession which freed him from the bitter worries about gaining a living His situation determined the choice of a profession He requested permission to enter and was accepted in 1843 in the Augustine Monastery [Augustiner-Stift] St Thomas in Altbrünn.

[1] Original in German published with comments by Dr Hugo Iltis in *Genetica*, 8:329–334, 1926 Present translation by Dr. Fritz Veit.

This step changed his material situation completely. With the physical comfort so conducive to any kind of study the respectful undersigned regained courage and vigour and he studied with much devotion and love the classical subjects prescribed for the trial year In his hours of leisure he occupied himself with the small botanical-mineralogical collection which he had available in the monastery His preference for the natural sciences grew and grew as he found increasing opportunity to become familiar with these subjects Although he lacked all oral direction in these studies and although in this field the autodidactic way is probably more tedious than in any other and although it leads to the attainment of the objectives quite slowly, he nevertheless acquired such a liking for the study of nature since that time that he will not refrain from any effort to fill the still existing gaps by self study as well as with the advice of experienced men. In 1846 he also attended the pertinent lectures on economics, fruit-tree culture and viticulture at the Academy for Philosophy [Philosophischen Lehranstalt] in Brünn. (Enclosure II, I, K.)

After the theological studies were completed in 1848 the respectful undersigned received permission from his Right Rev Prelate to prepare himself for the philosophical examinations [philosophischen Rigorosen] In the following year, when he was about to take the examinations, he was invited to accept the position of a substitute teacher at the Imperial-Royal Gymnasium in Znaim, and he accepted this call with pleasure. From the outset he endeavored to teach the various subjects entrusted to him in a manner which would be easily intelligible to his students, he hopes to have been successful in this, inasmuch as over a period of 4 years during which he had to earn his living as a tutor he had ample opportunity to obtain experiences relating to the achievements which might be expected of the students and to the differing degrees of youthful capacity for learning.

The respectful undersigned hopes that he herewith has given a brief sketch of his life history His sorrowful youth taught him early to appreciate the serious aspects of life, and to work Even while he enjoyed the fruits of secure economic conditions, the desire remained alive to earn the means for his own support. The respectful undersigned would consider himself happy if he could meet the requirements of the Worshipful Examination Commission and could attain fulfillment of his wish. He would not shrink from any endeavor and sacrifice to fulfill any duties in the most meticulous manner.

Znaim, April 17, 850 [sic]

Gregor Mendel
Suppl Professor
at the Imperial-Royal Gymnasium in Znaim

APPENDIX B

EXPERIMENTS RELATING TO PLANT HYBRIDS[1]

by

GREGOR MENDEL

(Presented at the meetings of February 8 and March 8, 1865)

Introductory Remarks

Artificial fertilization which was undertaken with ornamental plants in order to obtain new color variations was the occasion for the experiments that are to be discussed here. The striking regularity with which the same hybrid forms appeared again and again whenever the fertilization occurred between members of the same species was the stimulus to further experiments whose task it was to pursue the development of the hybrids in their descendants.

Careful observers such as Kolreuter, Gärtner, Herbert, Lecocq, Wichura and others have devoted to this task a part of their lives with indefatigable perseverance. Gärtner, especially, has reported very noteworthy observations in his work entitled "Die Bastarderzeugung in Pflanzenreiche" (The Production of Hybrids in the Plant Kingdom), and most recently Wichura published thorough experiments relating to hybrids of the willows. If one has not succeeded as yet in establishing a generally valid law for the formation and development of the hybrids it should not be astonishing to any one who is acquainted with the extent of the task and who knows how to appreciate the difficulties with which experiments of this kind have to cope. A final decision can be reached only when we have available detailed experiments from the most diverse plant families.

[1] Page 1 of Mendel's paper on peas. Translation by Dr Fritz Veit

LABORATORY EXERCISES IN GENETICS[1]

FOREWORD TO THE INSTRUCTOR

Genetics, like other branches of biology, is taught most effectively by means of demonstrations, observations, and experiments Carefully selected concrete objects arouse the interest and hold the attention of students as nothing else There is evidence that clarity of understanding and degree of retention of facts and principles vary directly with the extent of use of material objects On the basis of experience with numerous college classes the following laboratory exercises are offered as aids in the teaching of the elements of genetics The various items listed are classified under the principles which they illustrate. The sequence of topics corresponds to that of the chapters in the text

I. SEXUAL REPRODUCTION IN PLANTS

Students of genetics should have a clear understanding of the process of sexual reproduction in seed plants The basic laws of heredity were deduced from experiments with plants, and progress in genetics today involves experiments with plants as well as with animals.

As a means of reviewing the process of sexual reproduction in seed plants (it is assumed that students of genetics have considered the topic at some time in a previous course in biology or botany), the flower of the pea, either the edible pea or the sweet pea, both mature and immature, will be studied and dissected As an alternative to peas, bush beans may be used. The latter take about six weeks to grow from seeding to fruiting in a warm greenhouse. The flowers are similar to those of the pea.

Examine and identify the various parts of the flower, and review the functions of the parts Remove the pistil and a stamen from an immature flower and examine them under the microscope Crush an anther of a mature flower on a slide in a drop of water, add a cover glass, and observe pollen grains under high power Draw a pollen grain What characteristics of the flower of the pea favor self-pollination?

As a supplement to the study of flowers, large-scale models or charts, or lantern slides showing the essentials of reproduction in seed plants will be used

All of these studies should serve to emphasize the fact that modern genetics deals primarily with the consequences of sexual reproduction and development. It will be seen hereafter that gamete formation and fertilization are basically the same in plants and animals.

[1] The author is indebted to Dr Paul Glenister for useful suggestions in the preparation of these exercises

II. MENDEL'S FIRST LAW (SEGREGATION)

Peas

Obtain packages or samples of seeds of various varieties of peas: round yellow, round green, wrinkled yellow, wrinkled green, gray-brown seed-coated, etc. Note differences in color and form of seeds among the varieties as well as individual differences within a single variety.

Soak a seed of a round-seeded variety and one of a wrinkled variety overnight; remove the seed coats, noting the color of the seed coats and cotyledons. Crush a portion of the seed of each variety in a few drops of water and examine a drop of the suspension under high power. The instructor may issue suspensions as unknowns and ask you to identify the variety (as round or wrinkled) by comparison with the drawings on page 223 Make drawings of the two principal types of starch grains

Maize

Examine ears of several color varieties of Indian corn: yellow, white, red, purple, etc , also ears with filled seeds, shrunken seeds, starchy seeds, sugary seeds

Obtain ears which have been produced by self-pollination, showing on each ear a supposed monohybrid ratio of 3·1 for some pair of contrasting characters in color or seed form. Count one row at a time and record the number of seeds for each character If irregularities of rows make counting uncertain, mark each seed in turn with a dot of washable ink. (The procedure of marking rather than removing seeds is followed so that the ears may be used again. By storing the ears in a tight metal container, with an insect repellent, it is possible to keep the ears in good condition for years and to use them again and again.)

To the observed ratio on each ear apply the chi-square (χ^2) test as described in the text.

If available, also count seeds on ears produced by backcrossing the heterozygote to the recessive, giving an expected ratio of 1:1. Apply the χ^2 test as in the preceding study.

Seeds of maize and of sorghum produced by self-pollination of plants heterozygous for albinism are also obtainable When planted these seeds give rise to seedlings showing a ratio of 3 green:1 albino (see text page 182) To obtain satisfactory ratios, plant at least 100 seeds from stock not more than one or two years old. (If preferred this experiment may be deferred and combined with Exercise IX, on heredity and environment.)

Drosophila Experiments

Note to Instructor · Experiments with *Drosophila melanogaster* are highly instructive and easily carried out. If such experiments are to be done, it is strongly recommended that each student be provided with a copy of the excellent booklet "Drosophila Guide," by M. Demerec and B P. Kaufmann, published by the Carnegie Institution of Washington, 1530 P Street, N.W., Washington 5, D C, at 25 cents. This is an illustrated guide of 44 pages giving in full the life cycle of the fly, the methods of culturing, directions for handling matings and recording results, directions for the study of chromosomes, descriptions for carrying out

detailed matings of the monohybrid cross, the backcross, the dihybrid cross, linkage, sex linkage, the *ClB* cross, attached-x cross, determination of linkage groups, and selection experiments

The number of illustrative experiments that are done with Drosophila will of course depend upon the time available and the particular interests of the class. Since experiments with Drosophila require that matings be made well in advance

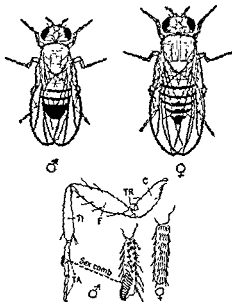


Figure 149. *Drosophila melanogaster*, male and female. (*From T. H. Morgan.*) Diagram of left foreleg of male, *below*, *detail at right*, metatarsus of male with its sex comb compared with the female, which lacks the sex comb (*From Demerec and Kaufmann, "Drosophila Guide,"* 1950.)

of the counting of F_2's in class, the writer commonly begins with a dihybrid mating involving the factor principle described hereinafter

III. MENDEL'S SECOND LAW (INDEPENDENT ASSORTMENT)

Ears of maize showing independent assortment of seed characters will be provided for study. Among those available showing clear-cut 9 : 3 : 3 : 1 ratios are the following: yellow starchy-white sweet, purple starchy-white sweet, white starchy-purple sweet. The last of these carries the dominant inhibitor of aleurone color. (The list of genes in maize (page 412) will be found very useful.)

Count and record the ratios of seeds on the ears as in the monohybrid crosses and apply the χ^2 test to the observed ratios.

IV. THE CHROMOSOME MECHANISM

Mitosis

Prepared slides of actively dividing cells of plants or animals, stained to show clearly numerous mitotic figures, will be provided for study. Among the best of such material obtainable in plants are sections of root tips of the onion (*Allium*) and the spiderwort (*Tradescantia*). For mitosis in animals the early cleavage stages in the roundworm (*Ascaris*) and the whitefish (*Coregonus*) are excellent.

An attempt should be made to identify on the slides all the stages described in the text In the case of the whitefish, the typical interphase is not found in the early stages of development; the cells pass directly from the late telophase into the early prophase. In root tips interphases are present. If the whitefish is used, polar views should be studied under the highest power available and an attempt made to estimate the number of chromosomes. With root tips the problem of counting chromosomes is not difficult, provided transverse sections are available.

Meiosis

(At the discretion of the instructor, the study of slides of meiosis may be deferred until the topic of sex determination is reached in the text.)

Before beginning the following study review the process of meiosis as described in Chaps 5 and 8.

Examine a slide showing stained sections of the testis of the squash bug, *Anasa tristis*, or of a grasshopper, under the highest power of the microscope available. The description that follows is based on the squash bug, although in essentials it may apply to the grasshopper also. The chromosome numbers will probably be different in the two forms.

Note that the testis is divided by partitions into several compartments Each compartment is a tubule. If the testis has been cut lengthwise, at one end, known as the upper end, each tubule will be seen to contain a number of rounded cysts; each cyst consists of numerous cells, the spermatogonia As the cysts move down the tubule these cells develop into spermatocytes, later into spermatids, and finally into mature sperms. Note mature sperms with deeply stained, elongated heads and long, slender, poorly stained tails near the lower end of the testis. In a given cyst all the cells are in approximately the same stage. In some of the cysts the cells will be seen in active mitosis; these cells may be spermatogonia, or primary or secondary spermatocytes. Some will be seen in polar view, others in equatorial view (Fig. 49).

Look for a cyst in which the primary spermatocytes are in prophase: the chromosomes are densely stained, synapsed in pairs, and lying close to the nuclear membrane. In some of these pairs chiasmata may be found (Fig 45). By focusing up and down you may see that the chromosomes are not lying in a single plane.

Find a metaphase plate stage of the first spermatocyte, showing 11 chromosomes lying in a single plane; 10 of these are synapsed pairs, and the eleventh is the single X chromosome (Fig. 49).

On some slides in certain tubules careful search will disclose one or more cells in late anaphase in equatorial view, showing one large chromosome lagging behind the others on the spindle This cell will probably be a second spermatocyte in anaphase and the lagging chromosome the undivided X (Fig 49) If such stages are rare, and a good example of it is found, the slide should be set up as a demonstration under the oil-immersion lens using an eyepiece of 15× or higher power for all to see.

Mature Gametes

Mature sperms and eggs of amphibians and mammals are used as demonstrations. While slides on meiosis are being studied, demonstration slides of the following will be set up by the instructor under separate microscopes. sections of ovary and testis of frog, showing gametes in various stages, ovary of cat, showing follicles with immature eggs of various sizes, section of guinea pig testis, showing tubules with spermatogenesis under way and with mature sperms in lumen, slides of stained sperms of the amphibian *Amphiuma*, of guinea pig, ram, and man

Make a sketch of a sperm of each species, all drawn to the same scale Make also a sketch of the eggs of frog and cat

V. THE FACTOR PRINCIPLE

Drosophila

The recessive eye-color mutants *brown* and *scarlet* (loci in chromosomes II and III, respectively) are mated, following the technique described in "Drosophila Guide" The F_1's will be wild type (red-eyed). Matings are made of the F_1's, and the F_2's are classified as to eye color The results should show an approximation to a 9.3:3·1 ratio of red, brown, scarlet, white. The double recessive develops no pigment in the eye A check of the classification of the flies, as made by students, will reveal the fact that people differ in their acuity of vision and in color discrimination for shades of red—discounting errors due to faulty technique. A color-blind or color-weak student will have difficulty with this experiment

Apply the χ^2 test to your observed ratio The instructor will calculate the χ^2 of the combined ratio for the class. Is there any indication that either mutant or double recessive is less viable than the wild type? Do any of the individual experiments suggest errors in classification of flies?

Maize

Observe ears of corn produced by self-pollination, showing on the cobs ratios of seed characters of the following. 9:3·4 purple-red-white, 9.7 purple-white, 13:3 nonpurple-purple, 12 3.1 white-purple-red

Besides the above dihybrid ratios, ears of the trihybrid ratio 27:37 purple-white and of the tetrahybrid ratio 81:27:148 purple-red-white are obtainable.

Apply the χ^2 test to the observed ratios.

VI. MULTIPLE ALLELES

Note to Instructor: As a demonstration of several series of alleles affecting coat color of mammals, a few cages of living rodents such as guinea pigs or mice are valuable Among the series especially recommended are the albino series and the agouti series in mice, and the albino series, the agouti series, and the red spotting series in the guinea pig

A useful collection of tanned skins showing a variety of coat colors similar to the above can be obtained by selection from the skins removed from cats dissected in the comparative-anatomy laboratory. The embalming process produces excellent pliable pelts with only the labor involved in tacking out, scraping, and salting the hides. After the skins are dried, the flesh side may be smoothed with sandpaper. (See list of genes of cat, page 447.)

Test for Blood Groups O, A, B, AB

Anti-A and anti-B sera, which are obtainable at reasonable cost from numerous laboratories and supply houses, are used for making this test. When the test is done for the purpose of making blood transfusions, special precautions are observed which it is not necessary for us to take. The test is simple and clear-cut. It may be carried out for the entire class in one hour or less by using the following simplified procedure·

1. Take a wad of absorbent cotton the size of the end of your thumb Moisten the cotton with 70 per cent alcohol. Rub the cotton thoroughly over the ball of one of your finger tips and over the pointed end of a fine sewing needle. Allow the sterile finger and needle to dry without letting them touch any object.

2. With a quick light jab puncture the sterile skin of finger tip and press out a small drop of blood

3. Obtain a plain slide marked at its opposite ends *anti-B* and *anti-A*, near each end of which has been placed a drop of normal salt solution (0 9 per cent NaCl)

4 Touch lightly the drop of blood to both drops of normal salt solution on the two ends of your slide and with your finger tip mix the blood and saline until you get homogeneous pink suspensions.

5. Place the slide on a piece of white paper. The instructor will add a drop of anti-B serum on one end of the slide and anti-A serum on the other end, according to the marks previously made on the slide

6. Tilt the slide gently from side to side to mix each serum with its cell suspension. After about one minute, small clots, visible with the naked eye, will begin to appear, provided the reaction is positive. The clots will increase in size, and after about three minutes the clumping of the red corpuscles is complete.

7. Compare your slide with Fig 36 in the text and determine your group Ask the instructor to check your slide before disposing of it.

8. If time permits, add cover slips and examine the slide under the microscope

9. Compare the percentages of the four blood groups found in the class with published data, making proper allowances for differences in gene frequencies in various racial and national populations.

VII. LINKAGE

A Two-point Experiment with Drosophila

The object of this exercise is to observe the behavior of linked genes in Drosophila and to compare the effects of linkage with those of independent assortment.

Make P_1 matings between males and virgin females using stocks carrying two mutant genes both of which have their loci on a single chromosome, either on chromosome II or chromosome III, as in Morgan's experiments (pages 121 and 122 in text).

Backcross the heterozygous F_1 females to homozygous double-recessive males.

Record the F_2's in a tabular form such as that suggested in "Drosophila Guide."

Apply the χ^2 test to your observed results, considering the map distance separating the genes chosen as the expected percentage of crossing over

Make the reciprocal of the above F_1 matings, i.e., backcross heterozygous F_1 males to double-recessive females, and record the F_2's.

Explain the differences in the results between the reciprocal matings

VIII. SEX LINKAGE

Drosophila Three-point Mating

An experiment with Drosophila involving three characters conditioned by factors in the X chromosome serves to demonstrate the peculiarities of sex-linked heredity, as well as the phenomena of linkage, and single and double crossovers Three such factors that have given good results are those for eosin eye color, miniature wing, and bar eye

Mate virgin eosin-miniature females with bar males The F_1's will all be bar females and eosin-miniature males This is an example of crisscross inheritance, found only in cases of sex-linked genes

Make F_1 matings (females need not be virgin) Record the F_2's in a form such as that suggested in "Drosophila Guide," listing first the two noncrossover types, next the crossovers between eosin and miniature, then the crossovers between miniature and bar, and lastly the two double-crossover types. Record each sex separately.

Apply the χ^2 test to the sex ratio obtained The percentage of crossing over between eosin and miniature and between miniature and bar should be calculated and compared with the map distances as shown on the Drosophila chromosome map (page 123) *Calculate the percentage of double crossovers; calculate the coincidence* (see Chap 8)

Color Blindness in Man

Note to Instructor: Students are tested individually for color blindness by means of the Ishihara plates or other similar devices. Those who are color-weak or color-blind are asked to read all the plates, and a record of such students is

occurs most frequently (the *mode*) and to multiply the number in each class by its deviation from the mode, either a negative deviation if smaller than the mode or a positive deviation if larger The algebraic sum of all the deviations from the mode divided by the total number of beans is added to the mode to obtain the

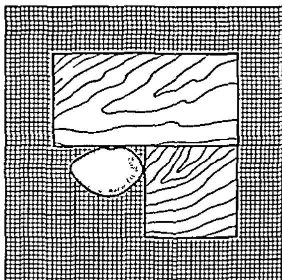


Figure 150. Device for rapid measurement of beans or other small objects.

true mean. For example, the mean breadth of the larger variety (Fig. 151) is calculated as follows.

$$\text{Mode} = 10$$

$$\text{Deviations: } [(13 \times 1) + (2 \times 2)] - [(33 \times 1) + (4 \times 2) + (5 \times 3)] =$$
$$17 - 56 = -39$$
$$-39 \div 100 = -0.39$$
$$\text{Mean} = 10 - 0.39 = 9.61.$$

For ready comparisons of the two varieties construct histograms showing the frequency for each size class Represent the frequencies vertically, with the class of smallest dimension on the left and the largest on the right, as in the accompanying diagram (Fig. 152)

The form of the histograms should be compared with those you have constructed for Problems 2 and 3 in Chap. 6, where the variability was assumed to be genetic in origin. With the beans we make no such assumption, and our data alone do not tell us whether the variability in length and width within a given variety is wholly environmental or not It is probable that the beans of a given variety purchased on the market are not identical with respect to all genes and that a part of the variability is therefore genetic. It is also certain that some of the variability is environmental, in the case of beans the environment includes such factors as position of the pod on the stem, position of the bean in the pod, etc.

Whatever the nature of the differential factors operating *within* a variety our study has shown that the frequency distribution approaches that theoretically expected of symmetrically acting plus and minus factors, as in the above-mentioned problems for height of men. Where numerous plus and minus factors distributed more or less at random affect developing organisms, the net result is often a curve of variability of the type obtained with the beans, approaching the *normal probability curve.* In this curve intermediate types are most numerous; there is a symmetrical falling off in numbers in both directions from the mean. The most extreme types are most rare.

Breadth, $\frac{1}{20}$ inch

Length, $\frac{1}{20}$ inch	6	7	8	Totals
11			//	2
10		卌 卌 /	卌 卌 卌 ////	30
9	卌 ///	卌 卌 卌 卌 卌 卌 卌 卌 ////	//	54
8	卌 卌	///		13
7	/			1
Totals	19	58	23	100

Small variety

Breadth, $\frac{1}{20}$ inch

Length, $\frac{1}{20}$ inch	7	8	9	10	11	12	Totals
17					//	/	3
16				//	卌 /	/	9
15			//	卌 卌 卌 卌	///		25
14			卌 卌 ///	卌 卌 卌 /	//		31
13		//	卌 卌 ////	卌			21
12			///				3
11			/				1
10	//	//					4
9	///						3
Totals	5	4	33	43	13	2	100

Large variety

Figure 151. Correlation tables (scatter diagrams) for two varieties of beans.

Naturally, hereditary factors are in part responsible for the differences between varieties. As mentioned above, the two varieties chosen should overlap at the extremes, i.e., the largest beans of the smaller variety should exceed in size the smallest beans of the larger variety. Now combine the data for the two

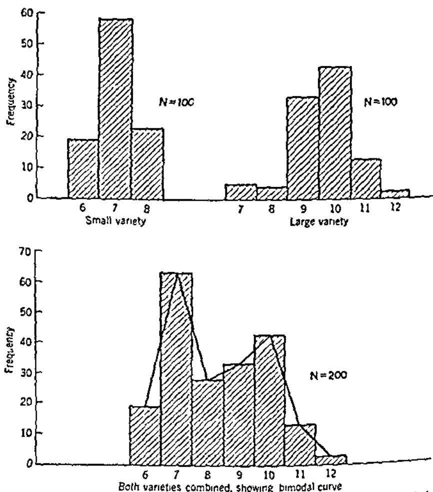


Figure 152. Histograms showing variation in width of beans. The numbers below the base line indicate twentieths of an inch.

varieties into a single histogram, as in Fig. 152. The resulting curve should be *bimodal*, namely, a curve with two peaks separated by a valley, as in Fig. 152.

In nature, measurements of populations of living things frequently display bimodal curves of variability; and when this happens we should suspect that the population is in *reality* a mixture of two populations differing in some major hereditary or environmental factor or factors. The bimodality may be due to sexual dimorphism, as in the case of human stature; adult males average several inches taller than females, with separate modes and much overlapping. Combin-

ing measurements of two races or varieties may give bimodal curves, curves for height of African Pygmies and their tall neighbors would no doubt illustrate bimodality A bimodal curve may indicate a mixture of two populations

In statistical studies the adequacy of the sample is of vital importance The sample must of course be chosen at random if a reliable result is expected there must be no bias in the selection of individuals for the sample. The sample must also be of adequate size, in general, the more variable the population in the character studied the larger the sample needed For example, in comparing the intelligence of two races of men, large samples are required, because intelligence is a highly variable trait, and with only a small sample one could not be satisfied that any differences observed represented accurately the real differences, if any, between the races

In order to obtain large samples of the varieties of beans, combine the data obtained by all students in the class The resulting histogram should be more nearly symmetrical than that of a single student's sample The range of variability is also likely to be greater than in the smaller samples The mean is likely to represent more accurately the true mean for the variety than does the mean obtained by any one student

X. HUMAN HEREDITY

Test of Taste for Phenylthiocarbamide

Students test themselves for taste sensitivity to PTC, using impregnated test paper, obtainable at nominal cost from the American Genetic Association, 1507 M Street, N W , Washington 5, D C The percentages of tasters and nontasters in the class are calculated and the percentages compared with the published data Students will also apply the test to members of their own families, if possible, including as many generations as possible Submit a copy of your pedigree thus obtained with your conclusion as to whether the results are in harmony with the theory of single gene difference in which inability to taste PTC is recessive

Form of Ear Lobes

Each student will observe his own and his desk partner's ear lobes and report on the following points

1. Can the lobes be clearly classified as free or attached (see Fig 117)?
2. Are the right and left lobes alike?
3. If the lobes do not clearly fall into one of the two categories, indicate by sketch or description their character

Obtain a pedigree of your own family respecting ear-lobe form and turn it in with problems at the end of *Chap 16*

GLOSSARY OF TERMS MOST COMMONLY USED IN GENETICS

Allele (al ēll') See **Allelomorph.**

Allelomorph (*allelon*, one another, *morphe*, form) One of two or more alternative hereditary units or genes or of the characters associated therewith, for example, the gene responsible for color blindness is an allelomorph of the alternative normal gene (Synonymous with **Allele.**)

Anaphase The stage of mitosis following the metaphase, characterized by the movement of the daughter chromosomes toward the poles of the spindle

Anther. A part of the stamen in seed plants consisting essentially of a spore case, in which the pollen develops It is usually borne on a slender stalk, the filament

Asexual (*a*, without, sex) Not involving gametes or fusion of nuclei, said of the mode of reproduction or of an individual restricted to such mode of reproduction

Atavism. See **Reversion.**

Autosome. Any chromosome other than a sex chromosome

Backcross The mating of a hybrid to one of the parental varieties or species which produced the hybrid

Bimodal. An adjective used to describe a frequency curve possessing two high points, peaks, or modes.

Centromere (kinetochore). A definite region of a chromosome which takes the lead in chromosome movements during mitosis and meiosis It is the point of spindle-fiber attachment

Character (a contraction of *characteristic*) Used to designate any structure, function, or trait of an organism The Mendelian characters represent the end products of development, in which a particular gene or genes have a specific effect

Chromatid. Either one of the two identical strands into which a chromosome splits in anticipation of cell division

Chromatin (*chroma*, color) A substance found in chromosomes which stains readily with "nuclear" or basic dyes

Chromomeres. The granules, visible especially during synapsis, arranged in definite linear order on the chromosome

Chromosomes (*chroma*, color, *soma*, body) Deeply staining bodies visible under the microscope in the cells, especially at the time of cell division The chromosomes consist essentially of genes, arranged in linear order.

Cross-fertilization. The union of a sperm from one individual with an egg from another individual

Crossing over. The exchange of corresponding blocks of genes between chromatids of homologous chromosomes resulting from breakage and fusion during synapsis, also applied to linked characters that show recombinations among the offspring of heterozygotes.

Cytology (*kytos*, cell, *logia*, study). The study of the structure and functions of the cell

Cytoplasm (cell, *plasm*, form) That part of the protoplasm of the cell outside of the nucleus

Dihybrid (*di*, two, hybrid) An individual which is hybrid (heterozygous) with respect to two pairs of genes.

Diploid (*diploos*, double) Referring to the double set of chromosomes, as found in the body cells of animals and the sporophyte generation of plants, as distinguished from the single (haploid) set, found in the mature reproductive cells

Dominant. A character which appears as the result of the presence of either a single or a double dose of a particular gene, as contrasted with the recessive, which develops only when both members of a pair of genes are alike. Applied also to the genes

Drift. Changes in the proportion of alleles in a population through the random (nonselective) loss of alleles, characteristic of small populations

Egg (ovum). A mature female reproductive cell formed by plants and animals which reproduce sexually In comparison with the male reproductive cell (sperm) it is very large, chiefly because of the stored food it contains

Endosperm. Nutritive tissue formed within the ovule in seed plants derived from the fusion of one of the sperm nuclei carried in the pollen tube with two of the nuclei of the ovule

Epistasis. The predominance of a gene over a nonallelic gene, the former is said to be *epistatic*, and the latter is *hypostatic*.

Equatorial plate The plate formed by the chromosomes lying on the equator of the spindle at metaphase.

Eugenics (*eugenes*, well born) The science concerned with the development and application of methods for the genetic improvement of the human species. "The study of agencies under social control that may improve or impair the racial qualities of future generations, either physically or mentally"—Sir Francis Galton, 1885

F_1 (ĕf-one). The first filial generation; offspring resulting from a crossing of two individuals that are homozygous for one or more pairs of distinguishing genes

F_2 (ĕf-two). The second filial generation produced by self-fertilization of the F_1 or the mating of F_1's.

Fertilization. The fusion of a sperm with an egg, forming a single cell, the zygote Fertilization has two effects. (1) it stimulates the egg to develop; (2) it combines two sets of genes in the embryo

Gamete. A mature germ cell, either an egg or a sperm

Gene. A unit of heredity which is transmitted in the chromosome and which, by interaction with other genes, the cytoplasm, and the environment, controls the development of a character, not subject to division by crossing over

Genetics. The branch of biology which deals primarily with the principles of heredity and secondarily with the role of environmental factors as they interact with the genes in the development of the individual

Genome. A chromosome set

Genotype. The complete genetic make-up of an individual, in contrast to the apparent, or visible, type of the individual (phenotype)

Germ cell. A cell capable of taking part in sexual reproduction as contrasted with the somatic, or body, cells, which are not able to do so A germ cell may be either the mature egg or sperm or an earlier cell capable of giving rise to one of these

Gonad. A reproductive gland, either male or female, a testis or an ovary In hermaphroditic animals it may be a compound gland (ovotestis)

Haploid (*haploos*, single) Referring to the reduced or single number of chromosomes, as found in the mature egg or the sperm, in contradistinction to the *diploid*, or double set of chromosomes, present in the body cells and early reproductive cells.

Hermaphrodite. An organism which produces both eggs and sperms False hermaphrodites are *intersexes*, having gonads of one sex only. See **Intersex.**

Heterogametic sex. The sex that produces two kinds of gametes with respect to sex determination, as the human male

Heterosis. See **Hybrid vigor.**

Heterozygote (*hetero*, different, *zygote*, egg) An organism whose parents contributed to it unlike genes affecting some inherited character, or which has unlike genes as a result of mutation, and which therefore produces gametes of two kinds with respect to such gene (The unlike genes may be any two of an allelic series) Such an organism is said to be *heterozygous*

Homogametic sex The sex that produces only one kind of gamete with respect to determination of sex

Homologous chromosomes. Chromosomes occurring in pairs, one member of each pair being normally derived from the egg and the other from the sperm

Homozygote (*homo*, same, *zygote*, egg) An organism which produces eggs or sperms of one kind only with respect to a particular series of alleles Such an organism is said to be *homozygous*

Hybrid An individual resulting from the union of a sperm and an egg which differ in one or more genes, e g , *Aa*, *AaBb*, *AaBbCc*, also used to denote the offspring of two distinct species or varieties

Hybrid vigor (heterosis) A phenomenon frequently noted as a result of the crossing of two distinct species, races, or varieties, the hybrid exceeding both parents in size, fecundity, resistance to parasites, or other adaptive quality

Identical twins. Two individuals developed from a single fertilized egg and therefore possessing identical sets of genes Such twins are about as much alike as

the right and left sides of the body of a single individual; also called monozygotic, or one-egg, twins

Inbreeding. The mating of related individuals such as first cousins or nearer of kin The automatic effect of inbreeding is to increase homogeneity, resulting in time in the production of a pure breed.

Independent assortment, principle of (Mendel's second law). The random combination of characters in the offspring as the result of the random alignment of the chromosomes on the equator of the spindle at the reduction division; their random combination in eggs and sperms; and independent union at fertilization Independent assortment occurs only when the genes affecting such characters are on separate (nonhomologous) chromosomes

Intersex. An individual showing characters intermediate between male and female It may be the result of a mutation, an abnormal chromosome complex, an endocrine disturbance, or environmental factors.

Lethal gene. A gene that renders an individual which expresses the gene unable to live Lethal genes are either dominant or recessive and may affect the organism at any stage of its development.

Linkage A tendency of certain characters to stick together in heredity because the genes for such characters are located on the same chromosome A group of linked characters or linked genes is called a linkage group; in each species there is the same number of linkage groups as chromosome pairs.

Locus. The position on a chromosome occupied by a gene or any of its alleles.

Maturation divisions. See **Meiosis.**

Meiosis (*meiosis*, reduction) A process consisting essentially of two successive cell divisions, resulting in cells having a single (haploid) set of chromosomes as contrasted with the double (diploid) set in the body cells In animals, meiosis occurs in the maturation of the gametes; in most plants it occurs in the formation of the spores

Metaphase. The middle stage in mitosis, in which the chromosomes are arranged in the equatorial plate.

Mitosis (*mitos*, thread) The usual type of cell division, involving the condensation of the chromatin into threads, the longitudinal splitting of the threads, their shortening into chromosomes consisting of pairs of chromatids, the division of the centromeres, and the movement of the chromosomes to the opposite poles of the cell Each daughter cell thus receives a full complement of chromosomes characteristic of the mother cell

Monohybrid (*mono*, single; hybrid). A hybrid with respect to only one pair of genes, as *Aa* or *Bb*

Mulatto. A hybrid resulting from the cross Negro × white; sometimes applied also to a person of mixed Negro-white blood of any degree or to one of mixed Negro-Indian blood

Multiple alleles (multiple allelomorphs). A series of three or more alternative forms of a gene occupying a single locus on a chromosome.

Mutation. A sudden change in a gene resulting in a new hereditary variation Originally used to include also all kinds of sudden hereditary variations resulting from gross chromosome changes.

Nucleus. A minute body composed of specialized protoplasm, found within the cells of all organisms except certain one-celled forms such as bacteria and blue-green algae. The nucleus, in contrast to the cytoplasm which surrounds it, is readily stained with basic dyes.

Oöcyte (*oön*, egg). The egg cell prior to the completion of the process of maturation.

Oögenesis (*oön*, egg). Formation of the egg from the oocyte.

Oögonia (*oön*, egg; *gonos*, offspring). The descendants of the primordial reproductive cells, found in the ovary. The ultimate generation of oögonia become oöcytes.

Ovary. In seed plants the enlarged part of the pistil containing the ovules; in animals the female gonad which produces the eggs.

Ovule. A many-celled spore case within the ovary of seed plants; it produces a large spore from which the egg develops.

Ovum. See **Egg.**

Parthenogenesis (*parthenos*, virgin). The development of an individual from an unfertilized egg, found normally in some invertebrates but rarely in vertebrates.

Pedigree. A record of the ancestry of an individual.

Penetrance (of a gene). The percentage of individuals possessing a certain gene who show some phenotypic effect of the gene.

Petal. One of the modified leaves of flowers, usually brightly colored, surrounding the stamens and pistil. The chief function of the petals is to attract insects.

Phenotype (*pheno*, appear, type). The organism as analyzed into its observable characters, as contrasted with its genetic constitution, or genotype.

Pistil. One of the reproductive organs in seed plants which consists of the stigma, or pollen receptor; the style, or connecting stalk, and the ovary.

Pleiotropic gene. A gene that produces two or more distinct effects in a single individual.

Polar body. A minute cell containing a normal single set of chromosomes but very little cytoplasm, cast off and discarded by the maturing egg in animals.

Pollen. Tiny structures produced in the anthers of seed plants, usually appearing as fine yellow dust. Each pollen grain is originally a single-celled spore, with a heavy wall. The spore nucleus divides, and one of the resulting nuclei divides again to produce the sperm nuclei.

Pollen tube. A microscopic tube which grows out from the pollen grain after the pollen lodges on the upper end of the pistil of the flower. At its tip the pollen tube carries along the two sperm nuclei, one of which fertilizes the egg in the ovule; the other unites with two other nuclei in the ovule to form the endosperm.

Pollination. The act of transferring pollen from the anther to the stigma of the flower.

Polyploid. An organism with one or more sets of homologous chromosomes in excess of the diploid number; e.g., a triploid with three sets, a tetraploid with four sets, etc.

Prophase. The stage in mitosis preceding the metaphase and characterized by the appearance of the chromosomes, the formation of the spindle, the break-up

of the nuclear membrane, and the movement of the chromosomes toward the equator of the spindle.

Protoplasm (*protos*, first, *plasm*, a thing formed). A complex organization of substances containing a large amount of water, proteins, other organic substances, and various salts—all together making up the "physical basis of life." The protoplasms of different organisms differ slightly in their proteins, etc Both nucleus and cytoplasm are made up of protoplasm.

Recessive. A character which appears only when both members of a pair of genes (or, in the case of polyploids, all the representatives of a locus) are alike, that is, in the homozygous condition, in contrast with the dominant, which develops in the presence of even a single dose of a gene. The term recessive is applied also to the genes

Reciprocal matings. Two matings between unlike individuals, in each mating one sex having the same characters as the opposite sex in the other mating.

Recombination. A new combination of linked characters in an individual as a result of crossing over in one or both of the parents; also applied to the individual that shows such a new combination.

Reduction division. A cell division that takes place in animals in the formation of the sperms and eggs and in plants in the formation of the spores, whereby the double set of chromosomes is reduced to a single set. See **Meiosis.**

Reversion (atavism). The sudden appearance of an individual which differs in some respect from its parents but resembles its grandparents or more distant ancestors

Secondary sexual character. A character normally dependent, either directly or indirectly, for its expression upon chromosome differences in the two sexes, but not necessarily having any direct reproductive function.

Segregation, principle of (Mendel's first law). The separation of the members of a pair of genes during meiosis and the random union of these with other genes at fertilization, resulting in the typical Mendelian ratios among the progeny.

Self-fertilization. The union of a sperm with an egg, both of which are produced by the same individual Of necessity, such individuals are hermaphroditic.

Sex chromosomes. Chromosomes concerned especially with the determination of sex. In most animals so far examined, and in some plants, the females have two X chromosomes and the male one X accompanied by its unmatched mate, the Y chromosome. In birds and some moths and fishes the male has two X chromosomes and the female has one X without a Y or one X and one Y. In some invertebrates the female has two X's and the male has one X and no Y.

Sex linkage. An association of a Mendelian character with sex in such a way that the character in certain matings crosses from one sex to the other. The cause of this result is the location of the gene for such character in the sex chromosome.

Somatic cells (*soma*, body; cells). All cells in the body except the germ-cell line. In animals and higher plants the somatic cells, with few exceptions, have the

double number of chromosomes; they take no part in the formation of eggs or sperms and in most species are therefore doomed to die eventually

Sperm (*sperma*, seed) The *spermatozoon*, or mature male germ cell

Spermatid (*sperma*, seed) One of the final generation of cells in meiosis, which, without further division, transforms into a sperm

Spermatocyte (*sperma*, seed; *kytos*, cell) One of the cells produced by the spermatogonia which undergoes two meiotic divisions to produce four spermatids

Spermatogenesis (*sperma*, seed; *genesis*, origin) The process of production of the sperms; sometimes limited to the process of meiosis

Spermatogonia (*sperma*, seed; *gone*, generation) The descendants of the primordial male reproductive cells which give rise to the spermatocytes

Spindle. A structure formed in the cytoplasm during mitosis and appearing to be made up of threads, or fibers, arranged in the form of a spindle

Spore. As applied to the higher plants, a single reproductive cell, produced asexually, not found in animals except Protozoa Spores in the higher plants contain a single set of chromosomes

Stamen. One of the reproductive organs of the flower consisting of the anther and filament; its function is the production of pollen

Stigma. The upper end of the pistil on which the pollen falls and germinates It is usually expanded and moist

Synapsis (*synapto*, to fuse together) The conjugation, or union, in pairs of homologous chromosomes of maternal and paternal origin, respectively It is the primary step in meiosis

Telophase (*telos*, end) The closing stage in mitosis during which the daughter nuclei are formed and cell division is completed

Testis The male reproductive gland in animals in which the sperms develop, synonymous with *testicle*

Tetrad (*tetras*, four) The group of four chromatids, the product of a pair of chromosomes, formed in the primary spermatocyte and primary oocyte

Unit character. A character which owes its difference from another character to a single gene difference The term is falling into disuse since it is now recognized that the gene rather than the character is the unit of heredity and that every character probably depends upon more than one gene

Variation A difference or differences, either hereditary or environmental, among individuals in a species

Variety. A subgroup within a species which differs in one or more genes from the rest of the species

X chromosome; Y chromosome. See **Sex chromosomes.**

Zygote (*zygotes*, yoked). The cell formed by the union of sperm and egg; the fertilized egg.

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Page references in boldface type indicate illustrations